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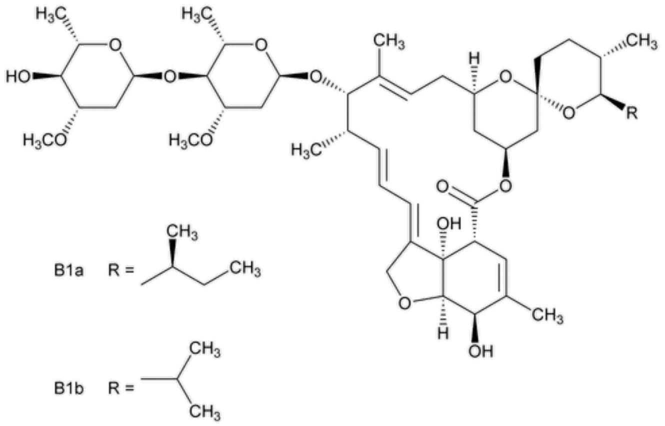
Ivermectin

Change to read:



$C_{48}H_{74}O_{14}$(Component H_2B_{1a}) ▲875.11▲ (ERR 1-Jul-2022)
$C_{47}H_{72}O_{14}$(Component H_2B_{1b}) ▲861.08▲ (ERR 1-Jul-2022)

Component H_2B_{1a}:
Avermectin A_{1a}, 5-*O*-demethyl-22,23-dihydro-.
(2a*E*,4*E*,8*E*)-(5'*S*,6*S*,6'*R*,7*S*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6'-(*S*)-*sec*-Butyl-3',4',5',6,6',7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy▲-5',6,8,19-tetramethyl-17-oxospiro▲ (ERR 1-Jul-2022) [11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'-[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside CAS RN®: ▲71827-03-7; UNII: 91Y2202OUW.▲ (ERR 1-Jul-2022)

Component H_2B_{1b}:
Avermectin A_{1a}, 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-.
(2a*E*,4*E*,8*E*)-(5'*S*,6*S*,6'*R*,7*S*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-3',4',5',6,6',7,10,11,▲14,15,17a,20,20a,20b-Tetradecahydro-20,20b-dihydroxy-6'-isopropyl-5',6,8,19-tetramethyl-17▲ (ERR 1-Jul-2022) -oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2'▲-▲ (ERR 1-Jul-2022) [2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside CAS RN®: 70209-81-3; UNII: 0W28CYI3TU.

» Ivermectin is a mixture of avermectin A_{1a}, 5-*O*-demethyl-22,23-dihydro-(component H_2B_{1a}), and avermectin A_{1a}, 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-(component H_2B_{1b}). It contains not less than 95.0 percent and not more than 102.0 percent for the sum of component H_2B_{1a} plus component H_2B_{1b}, calculated on the anhydrous and alcohol- and formamide-free basis; and the ratio (calculated by area percentage) of component $H_2B_{1a}/(H_2B_{1a} + H_2B_{1b})$ is not less than 90.0 percent. It may contain small amounts of suitable antioxidant and chelating agents.

Packaging and storage—Preserve in tight containers. Store between 2° and 8°. Where the use of an antioxidant is allowed, store at 25°, excursions permitted between 15° and 30°.

Labeling—If it is intended for veterinary use only, it is so labeled. Label it to state the name(s) and amount(s) of any added substance(s). Label it also to state that it is for manufacturing, processing, or repackaging.

USP Reference standards ⟨11⟩—
USP Ivermectin RS

Identification—

A: *Spectroscopic Identification Tests ⟨197⟩, Infrared Spectroscopy: 197K.*

B: The retention times of the component H_2B_{1a} peak and the component H_2B_{1b} peak in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Specific rotation ⟨781S⟩: between −17° and −20° measured at 20°, calculated on the water-, alcohol-, and formamide-free basis.

Test solution: 25 mg per mL, in methanol.

Water Determination, *Method I* ⟨921⟩ : not more than 1.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Limit of alcohol and formamide—

Internal standard solution—Dilute 0.5 mL of isopropyl alcohol with water to 100 mL, and mix.

Standard solution 1—Transfer 2.0 mL of dehydrated alcohol to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solution 2—Transfer 1.0 mL of formamide to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solution 3—Transfer 5.0 mL of *Standard solution 1* and 5.0 mL of *Standard solution 2* to a 50-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of formamide and alcohol of 0.001 and 0.002 mL per mL, respectively. Transfer 2.0 mL of this solution to a 15-mL centrifuge tube, add 2.0 mL of *m*-xylene, insert the stopper, mix, and centrifuge. Remove the upper *m*-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of *Internal standard solution,* and mix. Each mL of this solution contains about 0.0008 mL of alcohol and 0.0004 mL of formamide.

Standard solution 4—Transfer 10.0 mL of *Standard solution 1* and 10.0 mL of *Standard solution 2* to a 50-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of alcohol and formamide of 0.004 and 0.002 mL per mL, respectively. Transfer 2.0 mL of this solution to a 15-mL centrifuge tube, add 2.0 mL of *m*-xylene, insert the stopper, mix, and centrifuge. Remove the upper *m*-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of *Internal standard solution,* and mix. Each mL of this solution contains about 0.0016 mL of alcohol and 0.0008 mL of formamide.

Test solution—Transfer 120 mg of Ivermectin, accurately weighed, to a 15-mL centrifuge tube, and dissolve in 2.0 mL of *m*-xylene, heating in a water bath at 45 ± 5°, if necessary. Add 2.0 mL of water, mix, and centrifuge. Transfer the *m*-xylene layer to a 15-mL centrifuge tube, and extract with 2.0 mL of water. Discard the upper *m*-xylene layer, combine the two retained lower aqueous layers, add 1.0 mL of *Internal standard solution,* and mix.

Chromatographic system (see CHROMATOGRAPHY ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m fused-silica analytical column coated with a 3-µm G43 stationary phase. The carrier gas is helium, with a 10:1 split ratio and a linear velocity of about 35 cm per second. The chromatograph is programmed as follows. The column temperature is maintained at about 40° for 5 minutes after injection, then increased at a rate of 20° per minute to 180° and maintained at 180° for 2 minutes. The injection port temperature is maintained at about 220°, and the detector temperature is maintained at about 280°.

Procedure—Separately inject equal volumes (about 2 µL) of *Standard solution 3, Standard solution 4,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for alcohol, formamide, and isopropyl alcohol. Plot the ratios of the peak responses for alcohol and isopropyl alcohol and for formamide and isopropyl alcohol versus concentrations, in mL per mL, of alcohol and formamide, respectively, obtained from *Standard solution 3* and *Standard solution 4.* From the graphs so obtained, and using the ratios of the peak responses for alcohol and isopropyl alcohol and for formamide and isopropyl alcohol obtained from the chromatogram of the *Test solution,* determine the concentrations, *C,* of alcohol and formamide in the *Test solution.* [NOTE—In the event that the peak responses of the *Test solution* are significantly outside the ranges of peak responses obtained from *Standard solution 3* and *Standard solution 4,* prepare additional *Standard solutions,* and chromatograph them to obtain peak responses bracketing those obtained with the *Test solution.*] Calculate the percentages of alcohol and formamide in the portion of Ivermectin taken by the formula:

$$500{,}000CD/W$$

in which *C* is the concentration of alcohol or formamide, as appropriate, in mL per mL, in the *Test solution; D* is the density of alcohol (0.79) or formamide (1.13); and *W* is the weight, in mg, of Ivermectin taken: not more than 5.0% of alcohol and 3.0% of formamide are found.

Related compounds—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Proceed as directed for *Standard preparation* in the *Assay.*

Test solution—Use the *Assay preparation.*

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatogram of the *Test solution* for a period of time equivalent to twice the retention time of the main peak in the chromatogram obtained from the *Standard solution,* and measure the peak areas. Calculate the percentage of each impurity by the formula:

$$100r_i/(r_s - r_b)$$

in which r_i is the peak area for each individual impurity in the *Test solution* chromatogram; r_s is the sum of all peaks in the *Test solution* chromatogram; and r_b is the total area of all peaks in a blank chromatogram: not more than 2.5% is found for the sum of all peaks with a relative retention time of about 1.3 to 1.4 (corresponding to H_4B_{1a} isomers and $\Delta^{2,3}$ H_2B_{1a}); not more than 1% is found for the peak with a relative retention time of about 0.7 (corresponding to 8a-oxo-H_2B_{1a}); not more than 0.7% is found for the peak with a relative retention time of about 0.5 (corresponding to avermectin B_{1a}); not more than 0.5% is found for any other individual impurity peak; not more than 1% is found for the sum of all unidentified peaks; and not more than 4% is found for the sum of all the peaks, apart from the two main peaks (H_2B_{1a} and H_2B_{1b}). Disregard any peak that is calculated to be less than 0.05%.

Assay—

Mobile phase—Prepare a mixture of acetonitrile, methanol, and water (53:27.5:19.5), and degas. Make adjustments if necessary (see *System Suitability* under Chromatography ⟨621⟩). Increasing the proportion of water increases the elution times and allows better separation of impurities.

Standard preparation—Dissolve an accurately weighed quantity of USP Ivermectin RS in methanol to obtain a solution having a known concentration of about 0.4 mg per mL.

Assay preparation—Transfer about 40 mg of Ivermectin, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Sonicate, if necessary.

Chromatographic system (see Chromatography ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for component H_2B_{1b} and 1.0 for component H_2B_{1a}; the resolution, *R*, between component H_2B_{1b} and component H_2B_{1a} is not less than 3.0; the column efficiency determined from the component H_2B_{1a} peak is not less than 2000 theoretical plates; the tailing factor for component H_2B_{1a} peak is not more than 2.5; and the relative standard deviation for six replicate injections is not more than 1.0% determined from the component H_2B_{1a} peak.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for component H_2B_{1a} and component H_2B_{1b}. Calculate the quantity, in mg, of component H_2B_{1a} ($C_{48}H_{74}O_{14}$) and component H_2B_{1b} ($C_{47}H_{72}O_{14}$) in the portion of Ivermectin taken by the formula:

$$DC(r_U/r_S)$$

in which *D* is the dilution factor, in mL, used to prepare the *Assay preparation; C* is the concentration, in mg per mL, of component H_2B_{1a} or component H_2B_{1b} in the *Standard preparation;* and r_U and r_S are the peak areas for component H_2B_{1a} or component H_2B_{1b} obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

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Chromatographic Database Information: Chromatographic Database

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