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Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine

» Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of acetaminophen ($C_8H_9NO_2$), chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$), and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) or pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$].

[Note—The heading of this monograph does not constitute the official title. It is not intended that the name described herein be recognized as the official title or the common or usual name. The name for each article encompassed by this monograph shall be composed of the names of the active ingredients contained therein, as well as the quantitative amount of each active ingredient, and a statement of the function (or purpose) of the ingredient in the article.]

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—

- USP Acetaminophen RS
- USP Chlorpheniramine Maleate RS
- USP Dextromethorphan Hydrobromide RS
- USP Pseudoephedrine Hydrochloride RS
- USP Pseudoephedrine Sulfate RS

Labeling—The label for each article encompassed by this monograph bears a name composed of the active ingredients contained in the article. The label states the name and quantity of each active ingredient and indicates its function (or purpose) in the article.

Identification—

A: If pseudoephedrine hydrochloride or pseudoephedrine sulfate is purported to be present, the retention time of the major peak for pseudoephedrine in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for pseudoephedrine hydrochloride* or the *Assay for pseudoephedrine sulfate.*

B: If acetaminophen is claimed in the labeling to be present, the retention time of the major peak for acetaminophen in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for acetaminophen.*

C: If chlorpheniramine maleate is claimed in the labeling to be present, the retention time of the major peak for chlorpheniramine in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for chlorpheniramine maleate.*

D: If dextromethorphan hydrobromide is claimed in the labeling to be present, the retention time of the major peak for dextromethorphan in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for dextromethorphan hydrobromide.*

Dissolution, *Procedure for a Pooled Sample* ⟨711⟩—

Medium: water; 900 mL.

Apparatus 1: 100 rpm.

Time: 45 minutes.

Test preparation—Mix 9.0 mL of a filtered portion of the solution under test with 1.0 mL of 1% phosphoric acid solution.

Procedure—Determine the amounts of pseudoephedrine hydrochloride or pseudoephedrine sulfate (as appropriate), acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide dissolved, employing the procedures set forth in the *Assay for pseudoephedrine hydrochloride* or *Assay for pseudoephedrine sulfate, Assay for acetaminophen, Assay for chlorpheniramine maleate,* and *Assay for dextromethorphan hydrobromide,* respectively, making any necessary volumetric adjustments.

Tolerances—Not less than 75% *(Q)* of the labeled amounts of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) or pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$], acetaminophen ($C_8H_9NO_2$), chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), and dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$) are dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Assay for pseudoephedrine hydrochloride (where pseudoephedrine hydrochloride is the salt form used, if present in the formulation)—

Mobile phase, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride* under *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine*.

Chlorpheniramine standard preparation—Prepare as directed for *Standard preparation* in the *Assay for chlorpheniramine maleate.*

Dextromethorphan standard preparation—Prepare as directed for *Standard preparation* in the *Assay for dextromethorphan hydrobromide.*

System suitability solution 1 (for Capsules that contain either all four ingredients or a combination of three containing chlorpheniramine salt)—Mix equal volumes of the *Standard preparation* and the *Chlorpheniramine standard preparation.*

System suitability solution 2 (for Capsules that contain no chlorpheniramine)—Mix equal volumes of the *Standard preparation* and the *Dextromethorphan standard preparation.*

Assay preparation—Transfer not fewer than 10 Capsules, accurately counted, to a 500-mL volumetric flask. Add about 100 mL of water and 10 mL of 5% phosphoric acid, and gently heat until the Capsules are fully dispersed. Cool the solution to room temperature, dilute with water to volume, mix, and filter. Quantitatively dilute a portion of this solution, if necessary, with water to obtain a solution having a concentration of about 0.12 mg of pseudoephedrine hydrochloride per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the pseudoephedrine peaks. Calculate the quantity, in mg, of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the Capsules taken by the formula:

$$(CL/D)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Pseudoephedrine Hydrochloride RS in the *Standard preparation; L* is the labeled quantity, in mg, of pseudoephedrine hydrochloride in each Capsule; D is the concentration, in mg per mL, of pseudoephedrine hydrochloride in the *Assay preparation,* based on the number of Capsules taken, the labeled quantity, in mg, of pseudoephedrine hydrochloride in each Capsule and the extent of dilution; and r_U and r_S are the pseudoephedrine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for pseudoephedrine sulfate (where pseudoephedrine sulfate is the salt form used, if present in the formulation)—

Mobile phase, System suitability solutions, and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride* under *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine*.

Chlorpheniramine standard preparation—Prepare as directed for *Standard preparation* in the *Assay for chlorpheniramine maleate.*

Dextromethorphan standard preparation—Prepare as directed for *Standard preparation* in the *Assay for dextromethorphan hydrobromide.*

Standard preparation—Dissolve an accurately weighed quantity of USP Pseudoephedrine Sulfate RS in water to obtain a solution having a known concentration of about 3.0 mg per mL. Transfer 2.0 mL of this solution to a 25-mL volumetric flask, add 2.5 mL of methanol, dilute with 0.1% phosphoric acid to volume, and mix.

Assay preparation—Proceed as directed for the *Assay preparation* in the *Assay for pseudoephedrine hydrochloride* to obtain a solution having a concentration of about 0.24 mg of pseudoephedrine sulfate per mL.

Procedure—Proceed as directed for *Procedure* in the *Assay for pseudoephedrine hydrochloride.* Calculate the quantity, in mg, of pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$] in each Capsule taken by the formula:

$$(CL/D)(r_U/r_S)$$

in which the terms are as defined therein, pseudoephedrine sulfate being substituted for pseudoephedrine hydrochloride.

Assay for acetaminophen *(if present)*—

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and glacial acetic acid (79:20:1). Make adjustments, if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Standard preparation—Transfer about 25 mg of USP Acetaminophen RS, accurately weighed, to a 100-mL volumetric flask. Add 4 mL of methanol, and mix until solution is complete. Add 0.2 mL of phosphoric acid, dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.25 mg per mL.

Assay preparation—Transfer not fewer than 10 Capsules, accurately counted, to a 500-mL volumetric flask. Add about 100 mL of water and 10 mL of 5% phosphoric acid, and gently heat until the Capsules are fully dispersed. Cool the solution to room temperature, dilute with water to volume, and mix. Quantitatively dilute a portion of this solution, if necessary, with 0.1% phosphoric acid to obtain a solution having a concentration of about 0.25 mg of acetaminophen per mL.

Chromatographic system (see *Chromatography ⟨621⟩*)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for Procedure: the tailing factor for the acetaminophen peak is not greater than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the acetaminophen peaks. Calculate the quantity, in mg, of acetaminophen ($C_8H_9NO_2$) in each Capsule taken by the formula:

$$(CL/D)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Acetaminophen RS in the *Standard preparation; L* is the labeled quantity, in mg, of acetaminophen in each Capsule; D is the concentration, in mg per mL, of acetaminophen in each mL of the *Assay preparation*, based on the

number of Capsules taken, the labeled quantity, in mg, of acetaminophen in each Capsule, and the extent of dilution; and r_U and r_S are the acetaminophen peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for chlorpheniramine maleate *(if present)*—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride* under *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine*.

Standard preparation—Dissolve an accurately weighed quantity of USP Chlorpheniramine Maleate RS in water to obtain a solution having a known concentration of about 0.8 mg per mL. Quantitatively dilute a portion of this solution with 0.1% phosphoric acid to obtain a solution having a known concentration of about 8 µg per mL.

Assay preparation—Transfer not fewer than 10 Capsules, accurately counted, to a 500-mL volumetric flask. Add about 100 mL of water and 10 mL of 5% phosphoric acid, and gently heat until the Capsules are fully dispersed. Cool the solution to room temperature, dilute with water to volume, mix, and filter. Quantitatively dilute a portion of this solution, if necessary, with 0.1% phosphoric acid to obtain a solution having a concentration of about 8 µg of chlorpheniramine maleate per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms and measure the responses for the chlorpheniramine peaks. Calculate the quantity, in mg, of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) in each Capsule taken by the formula:

$$(CL/D)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Chlorpheniramine Maleate RS in the *Standard preparation; L* is the labeled quantity, in mg, of chlorpheniramine maleate in each Capsule; D is the concentration, in mg per mL, of chlorpheniramine maleate in each mL of the *Assay preparation,* based on the number of Capsules taken, the labeled quantity, in mg, of chlorpheniramine maleate in each Capsule, and the extent of dilution; and r_U and r_S are the chlorpheniramine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for dextromethorphan hydrobromide *(if present)*—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride* under *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine*.

Standard preparation—Dissolve an accurately weighed quantity of USP Dextromethorphan Hydrobromide RS in water to obtain a solution having a known concentration of about 0.4 mg per mL. Quantitatively dilute a portion of this solution with 0.1% phosphoric acid to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Transfer not fewer than 10 Capsules, accurately counted, to a 500-mL volumetric flask. Add about 100 mL of water and 10 mL of 5% phosphoric acid, and gently heat until the Capsules are fully dispersed. Cool the solution to room temperature, dilute with water to volume, mix, and filter. Quantitatively dilute a portion of this solution, if necessary, with 0.1% phosphoric acid to obtain a solution having a concentration of about 0.04 mg of dextromethorphan hydrobromide per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the dextromethorphan peaks. Calculate the quantity, in mg, of dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$) in each Capsule taken by the formula:

$$(370.33/352.32)(CL/D)(r_U/r_S)$$

in which 370.33 and 352.32 are the molecular weights of dextromethorphan hydrobromide monohydrate and anhydrous dextromethorphan hydrobromide, respectively; C is the concentration, in mg per mL, of USP Dextromethorphan Hydrobromide RS in the *Standard preparation; L* is the labeled quantity, in mg, of dextromethorphan hydrobromide in each Capsule; D is the concentration, in mg per mL, of dextromethorphan hydrobromide in each mL of the *Assay preparation,* based on the number of Capsules taken, the labeled quantity, in mg, of dextromethorphan hydrobromide in each Capsule, and the extent of dilution; and r_U and r_S are the dextromethorphan peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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Chromatographic Database Information: Chromatographic Database

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