Chlorpromazine Hydrochloride Oral Concentrate

Type of Posting	Notice of Intent to Revise
Posting Date	18-Dec-2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 4 Expert Committee

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Chlorpromazine Hydrochloride Oral Concentrate monograph.

The purpose of the revision is to widen the acceptance criteria in the test for *pH* <*791*> from 2.3-4.1 to 2.3-5.0.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison and Team Lead (301-998-6792 or hrj@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Chlorpromazine Hydrochloride Oral Concentrate

DEFINITION

Chlorpromazine Hydrochloride Oral Concentrate contains NLT 90.0% and NMT 110.0% of the labeled amount of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$).

[NOTE—Throughout the following analyses, protect sample specimens, the Reference Standard, and solutions containing them, by conducting the analyses without delay, under subdued light, or using low-actinic glassware.]

IDENTIFICATION

Change to read:

- **A.**

Standard solution: 0.2 mg/mL of USP Chlorpromazine Hydrochloride RS in methanol

Sample solution: Transfer a portion of Oral Concentration, equivalent to 20 mg of chlorpromazine hydrochloride, to a 125-mL separator. Add 10 mL of water and 2 mL of sodium hydroxide solution (1 in 2). Extract with three 30-mL portions of ▲ethyl ether.▲ (TBD) Filter the combined ▲ethyl ether▲ (TBD) extracts through anhydrous sodium sulfate. With the aid of a stream of nitrogen evaporate the ▲ethyl ether▲ (TBD) to about 5 mL. Quantitatively transfer the solution to a 40-mL centrifuge tube. Evaporate with a stream of nitrogen and mild heat to dryness. Dissolve the residue in 100 mL of methanol.

Chromatographic system

(See *Chromatography ⟨621⟩, General Procedures, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel

Spray reagent: Dissolve 100 mg of platinic chloride in 10 mL of 0.1 N hydrochloric acid, add 25 mL of potassium iodide solution (1 in 25), 0.5 mL of formic acid, and dilute with water to 100 mL.

Application volume: 15 µL

Developing solvent system: Freshly prepared mixture of ethyl acetate that has been saturated with ammonium hydroxide, ▲ethyl ether,▲ (TBD) and methanol (75:25:20)

Analysis

Samples: *Standard solution* and *Sample solution*

Develop the chromatogram in the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the chamber, air-dry, and spray with *Spray reagent*.

Acceptance criteria: The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*.

- **B. IDENTIFICATION TESTS—GENERAL ⟨191⟩, *Chemical Identification Tests, Chloride***

Sample solution: Dilute a portion of the Oral Concentrate with an equal volume of water.

Acceptance criteria: Meets the requirements

ASSAY

Change to read:

- **PROCEDURE**

Standard solution: 8 µg/mL of USP Chlorpromazine Hydrochloride RS in 0.1 N hydrochloric acid

Sample stock solution: Nominally 0.2 mg/mL of chlorpromazine hydrochloride from Oral Concentrate prepared as follows. Transfer a portion of Oral Concentrate, previously diluted if necessary, equivalent to

about 10 mg of chlorpromazine hydrochloride, to a 50-mL volumetric flask. Dilute with 0.1 N hydrochloric acid to volume.

Sample solution: Nominally 8 µg/mL of chlorpromazine hydrochloride from *Sample stock solution* prepared as follows. Pipet 10 mL of the *Sample stock solution* into a 250-mL separator, add about 20 mL of water, render alkaline with ammonium hydroxide, and extract with four 25-mL portions of ▲ethyl ether.▲ (TBD) Extract the combined ▲ethyl▲ (TBD) ether extracts with four 25-mL portions of 0.1 N hydrochloric acid, collecting the aqueous extracts in a 250-mL volumetric flask. Aerate to remove residual ▲ethyl▲ (TBD) ether, and add 0.1 N hydrochloric acid to volume.

Instrumental conditions

Mode: UV-Vis

Analytical wavelengths: Maximum absorbance at about 254 and 277 nm

Cell: 1 cm

Blank: 0.1 N hydrochloric acid

Analysis: Calculate the percentage of the labeled amount of chlorpromazine hydrochloride ($C_{17}H_{19}ClN_2S \cdot HCl$) in the portion of Oral Concentrate taken:

$$\text{Result} = [(A_{U1} - A_{U2})/(A_{S1} - A_{S2})] \times (C_S/C_U) \times 100$$

A_{U1} = absorbance of the *Sample solution*, 254 nm

A_{U2} = absorbance of the *Sample solution*, 277 nm

A_{S1} = absorbance of the *Standard solution*, 254 nm

A_{S2} = absorbance of the *Standard solution*, 277 nm

C_S = concentration of USP Chlorpromazine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of chlorpromazine hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Change to read:

- **Limit of Chlorpromazine Sulfoxide**

Chlorpromazine sulfoxide standard stock solution 1: 10.6 mg/mL of USP Chlorpromazine Hydrochloride RS in dilute hydrochloric acid (1 in 100)

Chlorpromazine sulfoxide standard stock solution 2: Transfer 5 mL of *Chlorpromazine sulfoxide standard stock solution 1* to a 50-mL volumetric flask. Add 2 mL of 30% hydrogen peroxide and heat at 60° for 10 min. Cool, and dilute with 1 M sodium bisulfite to volume.

Chlorpromazine sulfoxide standard solution: 1 mg/mL of chlopromazine sulfoxide prepared as follows. Transfer 10.0 mL of *Chlorpromazine sulfoxide standard stock solution 2* to a 60-mL separator, and add 2 mL of sodium hydroxide solution (1 in 2). Extract with three 30-mL portions of ▲ethyl ether.▲ (TBD) Filter the extracts through ▲ethyl▲ (TBD) ether-wetted anhydrous sodium sulfate into a 250-mL conical flask. Cautiously evaporate the extracts to dryness. Dissolve the residue in 10.0 mL of methanol, and filter if necessary.

Sample solution: Transfer a portion of Oral Concentration, equivalent of 20 mg of chlorpromazine hydrochloride, to a 125-mL separator. Add 10 mL of water and 2 mL of sodium hydroxide solution (1 in 2). Extract with three 30-mL portions of ▲ethyl ether.▲ (TBD) Filter the combined ▲ethyl▲ (TBD) ether extracts

through anhydrous sodium sulfate. With the aid of a stream of nitrogen evaporate the ▲ethyl▲ (TBD) ether to about 5 mL. Quantitatively transfer the solution to a 40-mL centrifuge tube. Evaporate with a stream of nitrogen and mild heat to dryness. Dissolve the residue in 1.0 mL of methanol.

Chromatographic system

(See *Chromatography ⟨621⟩, Procedures, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel

Spray reagent: Dissolve 100 mg of platinic chloride in 10 mL of 0.1 N hydrochloric acid, add 25 mL of potassium iodide solution (1 in 25), 0.5 mL of formic acid, and dilute with water to 100 mL.

Application volume: 15 µL

Developing solvent system: Freshly prepared mixture of ethyl acetate that has been saturated with ammonium hydroxide, ▲ethyl ether,▲ (TBD) and methanol (75:25:20)

Analysis

Samples: *Chlorpromazine sulfoxide standard solution* and *Sample solution*

Develop the chromatogram in the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the chamber, air-dry, and spray with *Spray reagent*.

Acceptance criteria: The chromatogram from the *Sample solution* may exhibit a secondary spot whose R_F value corresponds to, and whose size and intensity are not greater than, those of the spot of the *Chlorpromazine sulfoxide standard solution* (5.0%).

SPECIFIC TESTS

- **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** It meets the requirements for the absence of *Escherichia coli*.

Change to read:

- **pH ⟨791⟩:** 2.3–▲5.0▲ (TBD)

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers.
- **Labeling:** Label it to indicate that it must be diluted prior to administration.
- **USP Reference Standards ⟨11⟩**

USP Chlorpromazine Hydrochloride RS

Page Information:

Not Applicable

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