Clomipramine Hydrochloride Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	28–Jul–2017
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Expert Committee	Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts, this is to provide notice that the USP Chemical Medicines Monographs 4 Expert Committee intends to revise the Clomipramine Hydrochloride Capsules monograph.

Comments with supporting data were received that indicate the existing Dissolution test is not suitable for all Clomipramine Hydrochloride Capsules. The Expert Committee proposes to revise the Clomipramine Hydrochloride Capsules monograph to add *Dissolution Test 2* to accommodate drug products which are anticipated to be approved with different dissolution conditions and acceptance criteria. A labeling requirement for tests other than *Dissolution Test 1* is also proposed for inclusion.

- *Dissolution Test 2* was validated using a Inertsil ODS 3V brand of column with L1 packing. The typical retention time for clomipramine is about 4 min.

It is anticipated that the proposed revision will be published as a Revision Bulletin. This revision is contingent on FDA approval of a drug product that meets the proposed monograph.

Should you have any questions, please contact Heather Joyce, Ph.D.**,** Senior Scientific Liaison to the Chemical Medicines Monographs 4 Expert Committee (301–998–6792 or hrj@usp.org).

Clomipramine Hydrochloride Capsules

DEFINITION

Change to read:

Clomipramine Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% of ▸the labeled amount of◂ (TBD) clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$).

IDENTIFICATION

• **A. INFRARED ABSORPTION** ⟨197K⟩

Sample: Transfer the contents of a number of Capsules, equivalent to about 125 mg of clomipramine hydrochloride, to a suitable container. Add 25 mL of chloroform, stir for 5 min, and filter. Evaporate on a steam bath to a volume of 5 mL, chill in an ice bath, add ethyl ether, and stir until crystals form. Filter, and dry at 100° for 1 h.

Acceptance criteria: Meet the requirements

ASSAY

• **PROCEDURE**

Solution A: 55 g/L of sodium 1-heptanesulfonate prepared as follows. Transfer a suitable quantity of sodium 1-heptanesulfonate to an appropriate volumetric flask. Dissolve in 50% of the flask volume of water, and dilute with glacial acetic acid to volume.

Mobile phase: Transfer 20.0 mL of *Solution A* and 2.0 mL of triethylamine to a 500-mL volumetric flask, and dilute with water to volume. Transfer this solution to a 1-L volumetric flask, adjust with phosphoric acid to a pH of 3.2 ± 0.1, dilute with acetonitrile to volume, filter, and degas.

System suitability solution: 0.07 mg/mL of USP Desipramine Hydrochloride RS and 0.10 mg/mL of USP Imipramine Hydrochloride RS in methanol

Standard solution: 0.32 mg/mL of USP Clomipramine Hydrochloride RS in methanol

Sample stock solution: Nominally 0.8 mg/mL of clomipramine hydrochloride from the contents of NLT 20 Capsules in methanol prepared as follows. Transfer a suitable quantity of the contents of Capsules to an appropriate volumetric flask. Add 65% of the flask volume of methanol, shake by mechanical means for 1 h, and dilute with methanol to volume.

Sample solution: Nominally 0.32 mg/mL of clomipramine hydrochloride from *Sample stock solution* in methanol prepared as follows. Transfer a suitable portion of *Sample stock solution* to an appropriate volumetric flask, dilute with methanol to volume, and filter. Use the filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 3.9-mm × 30-cm; packing L1
Flow rate: 1 mL/min
Injection volume: 10 µL

System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for desipramine and imipramine are 0.85 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 0.5 between desipramine and imipramine
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Clomipramine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of clomipramine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

▸**Test 1**◂ (TBD)
Medium: ▸0.1 N hydrochloric acid VS;◂ (TBD) 500 mL
Apparatus 2: 50 rpm
Time: 30 min
Standard solution: USP Clomipramine Hydrochloride RS in *Medium*
Sample solution: Sample per *Dissolution* ⟨711⟩, and filter the resulting solution. Dilute with *Medium*, if necessary, to a concentration that is similar to the *Standard solution*.
Instrumental conditions
Mode: UV
Analytical wavelength: Maximum absorbance at about 252 nm
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) dissolved.
Tolerances: NLT 80% (*Q*) of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) is dissolved.

▸**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 0.01 N hydrochloric acid TS; 500 mL
Apparatus 2: 75 rpm with sinkers
Time: 15 min
Solution A: 55 g/L of sodium 1-heptanesulfonate in solution prepared as follows. Transfer a suitable amount of sodium 1-heptanesulfonate to an appropriate volumetric flask. Add 50% of the flask volume of water and dilute with glacial acetic acid to volume.
Solution B: To an appropriate volumetric flask, add 4% of the flask volume of *Solution A* and 0.4% of the flask volume of triethylamine. Dilute with water to volume.
Mobile phase: To an appropriate volumetric flask, add 50% of the flask volume of *Solution B*. Adjust the resulting solution with phosphoric acid to a pH of 3.2. Dilute with acetonitrile to volume.
Standard stock solution: 0.5 mg/mL of USP Clomipramine Hydrochloride RS in *Medium*. Sonication may be used to promote dissolution.
Standard solution: (*L*/500) mg/mL of USP Clomipramine Hydrochloride RS from the *Standard stock solution* in *Medium*, where *L* is the label claim in mg/Capsule

Sample solution: Pass a portion of the solution under test through a suitable filter and discard NLT the first 5 mL of filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: NLT 1.4 times the retention time of clomipramine

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: 0.8–2.0
Relative standard deviation: NMT 1.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Clomipramine Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of the *Medium*, 500 mL
L = label claim of clomipramine hydrochloride (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) is dissolved.◄ (TBD)

- **Uniformity of Dosage Units** ⟨905⟩
Procedure for content uniformity
Standard solution: 30 µg/mL of USP Clomipramine Hydrochloride RS in methanol
Sample stock solution: Transfer the contents of 1 Capsule to a 100-mL volumetric flask with the aid of methanol. Add about 75 mL of methanol, shake by mechanical means for 1 h, and dilute with methanol to volume.
Sample solution: Nominally 30 µg/mL of clomipramine hydrochloride from the *Sample stock solution* in methanol
Instrumental conditions
Mode: UV
Analytical wavelength: Maximum absorbance at about 252 nm
Cell: 1 cm
Blank: Methanol
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of clomipramine hydrochloride ($C_{19}H_{23}ClN_2 \cdot HCl$) in the portion of Capsules taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (µg/mL)
C_U = nominal concentration of the *Sample solution* (µg/mL)

Acceptance criteria: Meet the requirements

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.

Add the following:

►• **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.◄ (TBD)
- **USP Reference Standards** ⟨11⟩
USP Clomipramine Hydrochloride RS
USP Desipramine Hydrochloride RS
USP Imipramine Hydrochloride RS