Clomipramine Hydrochloride Capsules

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Clomipramine Hydrochloride Capsules monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate drug products which have been approved with different dissolution conditions and acceptance criteria. A labeling requirement for tests other than *Dissolution Test 1* is also added.

- *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.

The Clomipramine Hydrochloride Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (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• (RB 19-Jan-2018) 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**• (RB 19-Jan-2018)
Medium: •0.1 N hydrochloric acid VS;• (RB 19-Jan-2018) 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 solu-*

tion 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.● (RB 19-Jan-2018)

• **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.● (RB 19-Jan-2018)

• **USP Reference Standards** ⟨11⟩
USP Clomipramine Hydrochloride RS
USP Desipramine Hydrochloride RS
USP Imipramine Hydrochloride RS