Clomipramine Hydrochloride Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	29–May–2020
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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 and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Clomipramine Hydrochloride Capsules monograph.

Based on the supporting data received from manufacturers awaiting FDA approval, the Expert Committee proposes to allow the use of suitable sinkers with *Dissolution Test 1*, when needed.

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 to the Chemical Medicines Monographs 4 Expert Committee (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*.

Clomipramine Hydrochloride Capsules

DEFINITION

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

IDENTIFICATION

● **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

● **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

● **Procedure**

Solution A: Add 2.5 mL of acetic acid to 1 L of water. Adjust with stronger ammonia water to a pH of 7.5.

Solution B: Acetonitrile, methanol, and stabilizer-free tetrahydrofuran (80:15:5)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0.0	65	35
2.0	65	35
5.0	50	50
11.0	20	80
14.0	20	80
14.1	65	35
18.0	65	35

Diluent: *Solution A* and acetonitrile (50:50)

System suitability solution: 0.2 mg/mL of USP Clomipramine Hydrochloride RS and 0.005 mg/mL of USP Clomipramine Related Compound A RS in *Diluent*

Standard solution: 0.2 mg/mL of USP Clomipramine Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of clomipramine hydrochloride from Capsules in *Diluent* prepared as follows. Transfer a sufficient portion of the contents of Capsules (NLT 20) to a suitable volumetric flask. Add 60% of the final flask volume of *Diluent*. Shake by mechanical means for about 30 min. Dilute with *Diluent* to volume. Centrifuge to obtain a clear supernatant and use the clear supernatant. [Note—The use of a centrifuge speed of 3000 rpm for 10 min may be suitable.]

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 254 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Column temperature: 30°

Flow rate: 0.3 mL/min

Injection volume: 2 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between clomipramine and clomipramine related compound A, *System suitability solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

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

Medium: 0.1 N hydrochloric acid VS; 500 mL

Apparatus 2: 50 rpm. ▲With suitable sinkers, if needed.▲ (TBD)

Time: 30 min

Standard solution: USP Clomipramine Hydrochloride RS in *Medium*

Sample solution: Pass the solution under test through a suitable filter and use the filtrate. Dilute with *Medium*, if necessary, to a concentration that is similar to the *Standard solution*.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 252 nm

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:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 500 mL

L = label claim (mg/Capsule)

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.

- **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

(See *Ultraviolet-Visible Spectroscopy ⟨857⟩*.)

Mode: UV

Analytical wavelength: 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 Capsule 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 USP Clomipramine Hydrochloride RS in the *Standard solution* (µg/mL)

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

Acceptance criteria: Meet the requirements

IMPURITIES

- **Organic Impurities**

Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 0.5 mg/mL of USP Clomipramine Hydrochloride RS and 0.0025 mg/mL of USP Clomipramine Related Compound A RS in *Diluent*

Standard solution: 0.0025 mg/mL each of USP Clomipramine Hydrochloride RS, USP Clomipramine Related Compound C RS, and USP Imipramine Hydrochloride RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of clomipramine hydrochloride from Capsules in *Diluent* prepared as follows. Transfer a sufficient portion of the contents of Capsules (NLT 20) to a suitable volumetric flask. Add 60% of the final flask volume of *Diluent*. Shake by mechanical means for about 30 min. Dilute with *Diluent* to volume. Centrifuge to obtain a clear supernatant and use the clear supernatant. [Note—The use of a centrifuge speed of 3000 rpm for 10 min may be suitable.]

System suitability

Samples: *System suitability solution* and *Standard solution*

[NOTE—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between clomipramine and clomipramine related compound A, *System suitability solution*

Relative standard deviation: NMT 5.0% for all standard peaks, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each specified impurity in the portion of Capsules taken:

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

r_U = peak response of each specified impurity from the *Sample solution*

r_S = peak response of the corresponding USP Reference Standard from the *Standard solution*

C_S = concentration of the corresponding USP Reference Standard in the *Standard solution* (mg/mL)

C_U = nominal concentration of clomipramine hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of each unspecified impurity in the portion of Capsules taken:

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

r_U = peak response of each unspecified impurity from the *Sample solution*

r_S = peak response of clomipramine 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: See *Table 2*. The reporting threshold is 0.03%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Imipramine	0.77	1.0
Clomipramine related compound C	0.87	0.5
Clomipramine	1.00	—
Clomipramine related compound A[a]	1.1	—
Clomipramine related compound D[a,b]	1.2	—
Clomipramine related compound F[a,c]	1.5	—
Any individual unspecified impurity	—	0.5
Total impurities	—	2.0

[a] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

[b] 3-(3,7-Dichloro-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

[c] 3-Chloro-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Protect from moisture. Store at controlled room temperature.
- **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Clomipramine Hydrochloride RS

USP Clomipramine Related Compound A RS

N^1-[3-(3-Chloro-10,11-dihydro-5*H*-dibenzo[*b,f*]azepin-5-yl)propyl]-N^1,N^3,N^3-trimethylpropane-1,3-diamine dihydrochloride.

$C_{23}H_{32}ClN_3 \cdot 2HCl$ 458.89

USP Clomipramine Related Compound C RS

3-(3-Chloro-5*H*-dibenzo[*b,f*]azepin-5-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride, monohydrate.

$C_{19}H_{21}ClN_2 \cdot HCl \cdot H_2O$ 367.31

USP Imipramine Hydrochloride RS

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