Clomipramine Hydrochloride Capsules

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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 an 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**

Clomipramine Hydrochloride Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of clomipramine hydrochloride (C₁₉H₂₃ClN₂·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 Clomipramine Hydrochloride RS and 0.1 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
  - **Resolution**: NLT 0.5 between desipramine and imipramine

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**
  - **Test 1**: Medium: 0.1 N hydrochloric acid VS; 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 (C₁₉H₂₃ClN₂·HCl) in capsules taken:**
    \[
    \text{Result} = \left(\frac{r_1}{r_2}\right) \times \left(\frac{C_s}{C_l}\right) \times 100
    \]
    \(r_1\) = peak response from the Sample solution
    \(r_2\) = peak response from the Standard solution
    \(C_s\) = concentration of USP Clomipramine Hydrochloride RS in the Standard solution (mg/mL)
    \(C_l\) = nominal concentration of clomipramine hydrochloride in the Sample solution (mg/mL)

**Acceptance criteria**: 90.0%–110.0%

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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 (C₁₉H₂₃ClN₂·HCl) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \frac{C_S}{V} \times \left( \frac{1}{L} \right) \times 100
\]

- \(r_U\): 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 (C₁₉H₂₃ClN₂·HCl) is dissolved.

**ADDITONAL 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.
- **USP Reference Standards (11)**
  - USP Clomipramine Hydrochloride RS
  - USP Desipramine Hydrochloride RS
  - USP Imipramine Hydrochloride RS