Cyclobenzaprine Hydrochloride Tablets

Type of Posting	Revision Bulletin
Posting Date	29–Jan–2016
Official Date	01–Feb–2016
Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Cyclobenzaprine Hydrochloride Tablets monograph. The purpose for the revision is to revise the test for *Organic Impurities* as follows:

- To widen the limit for cyclobenzaprine *N*-oxide from NMT 0.15% to NMT 0.2% to be consistent with the specification for an approved drug product
- To identify dibenzocycloheptenone as a process impurity which does not need to be included in the calculation of Total degradation products
- To clarify how to calculate all the specified and unspecified degradation products by removing the word “unspecified” from the calculation provided

Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Cyclobenzaprine Hydrochloride Tablets Revision Bulletin supersedes the currently official Cyclobenzaprine Hydrochloride Tablets monograph. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 39–NF 34*.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison, (301–998–6792 or HRJ@usp.org.)

Cyclobenzaprine Hydrochloride Tablets

DEFINITION

Cyclobenzaprine Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of cyclobenzaprine hydrochloride ($C_{20}H_{21}N \cdot HCl$).

IDENTIFICATION

- **A. Infrared Absorption** ⟨197M⟩
  Sample: Transfer an amount equivalent to 50 mg of cyclobenzaprine hydrochloride from a quantity of finely powdered Tablets to a small flask. Add 10 mL of methylene chloride, swirl to dissolve, and filter. Evaporate the clear filtrate to about 5 mL, transfer to a centrifuge tube, and add 1–2 mL of ether. Evaporate with the aid of a current of air to about 1 mL, and agitate until crystallization occurs. Wash the crystals with several portions of ether, and air-dry.
  Acceptance criteria: Meet the requirements
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**
  Buffer: 11.4 g/L of ammonium acetate in water. Adjust with ammonium hydroxide to a pH of 7.2.
  Mobile phase: Methanol and *Buffer* (65:35)
  Standard solution: 0.2 mg/mL of USP Cyclobenzaprine Hydrochloride RS in *Mobile phase*. Sonication may be used to aid in dissolution.
  Sample solution: Nominally 0.2 mg/mL of cyclobenzaprine hydrochloride from NLT 20 finely powdered Tablets in *Mobile phase* prepared as follows. Transfer a suitable amount of the powder to a suitable volumetric flask. Add 60% of the flask volume of *Mobile phase*, and sonicate for 30 min. Allow the solution to cool to room temperature, and then dilute with *Mobile phase* to volume. Centrifuge the solution, and use the supernatant.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 226 nm
  Column: 4.6-mm × 25-cm; 5-µm packing L7
  Column temperature: 30°
  Flow rate: 1 mL/min
  Injection volume: 10 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 0.85%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of cyclobenzaprine hydrochloride ($C_{20}H_{21}N \cdot HCl$) in the portion of Tablets 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 Cyclobenzaprine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of cyclobenzaprine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 1: 50 rpm
  Time: 30 min
  Sample solution: Pass a portion of the solution under test through a suitable filter, and dilute with *Medium* if necessary.
  Standard solution: USP Cyclobenzaprine Hydrochloride RS in *Medium* with a concentration similar to the one expected in the *Sample solution*
  Instrumental conditions
  (See •*Ultraviolet-Visible Spectroscopy* ⟨857⟩.)• (CN 1-May-2016)
  Mode: UV
  Analytical wavelength: 290 nm
  Analysis
  Samples: *Sample solution* and *Standard solution*
  Calculate the percentage of the labeled amount of cyclobenzaprine hydrochloride ($C_{20}H_{21}N \cdot HCl$) dissolved:

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

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Cyclobenzaprine Hydrochloride RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

  Tolerances: NLT 75% (*Q*) of the labeled amount of cyclobenzaprine hydrochloride ($C_{20}H_{21}N \cdot HCl$) is dissolved.
- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

- **Organic Impurities**
  Buffer and **Mobile phase:** Proceed as directed in the *Assay*.
  Standard solution: 0.6 µg/mL each of USP Cyclobenzaprine Hydrochloride RS, USP Cyclobenzaprine Related Compound A RS, and USP Cyclobenzaprine Related Compound B RS in *Mobile phase*
  Sample solution: Nominally 400 µg/mL of cyclobenzaprine hydrochloride from NLT 20 finely powdered Tablets in *Mobile phase* prepared as follows. Transfer a suitable amount of the powder to a suitable volumetric flask. Add 75% of the flask volume of *Mobile phase*, and sonicate for 30 min. Allow the solution to cool to room temperature, and then dilute with *Mobile phase* to volume. Centrifuge the solution, and use the supernatant.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC
Detector: UV 226 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 3 times the retention time of cyclobenzaprine

System suitability
Sample: *Standard solution*
[NOTE—See *Table 1* for relative retention times.]
Suitability requirements
Resolution: NLT 2.0 between the cyclobenzaprine related compound A and cyclobenzaprine related compound B peaks
Relative standard deviation: NMT 2.0% for the cyclobenzaprine peak

Analysis
Sample: *Standard solution* and *Sample solution*
•Calculate the percentage of any individual degradation product• (ERR 1-Dec-2015) in the portion of Tablets taken:

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

r_U = • peak response of any individual degradation product from the *Sample solution*• (ERR 1-Dec-2015)
r_S = peak response of cyclobenzaprine from the *Standard solution*
C_S = concentration of USP Cyclobenzaprine Hydrochloride RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of cyclobenzaprine hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria NMT (%)
Cyclobenzaprine related compound A[a]	0.51	—
Cyclobenzaprine related compound B[a]	0.59	—
Cyclobenzaprine *N*-oxide[b]	0.74	•0.2• (RB 1-Feb-2016)
Cyclobenzaprine	1.0	—
Amitriptyline[a,c]	1.3	—
Dibenzocycloheptenone •[a,]• (RB 1-Feb-2016)[d]	1.6	•—• (RB 1-Feb-2016)
Any individual unspecified degradation product	—	0.1
Total degradation products	—	2.0

[a] Process impurity included for identification only and not included in the calculation of total degradation products.
[b] 3-(5*H*-Dibenzo[*a,d*]cycloheptene-5-ylidene)-*N,N*-dimethyl-1-propanamine *N*-oxide.
[c] 10,11-Dihydro-*N,N*-dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,\gamma}$,-propylamine.
[d] Dibenzo[*a,d*]cycloheptene-5-one.

Table 1 *(Continued)*

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

Change to read:

- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Cyclobenzaprine Hydrochloride RS
USP Cyclobenzaprine Related Compound A RS
5-[3-(Dimethylamino)propyl]• (RB 1-Feb-2016)-5*H*-dibenzo[*a,d*]-cyclohepten-5-ol.
$C_{20}H_{23}NO$ 293.40
USP Cyclobenzaprine Related Compound B RS
3-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-*N*-methyl-1-propanamine•hydrochloride.
$C_{19}H_{19}N \cdot HCl$ 297.82• (RB 1-Feb-2016)