Cyclobenzaprine Hydrochloride

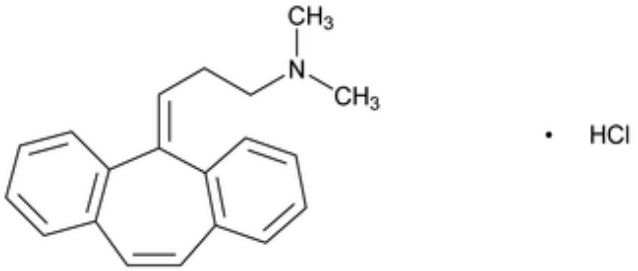
Type of Posting	Revision Bulletin
Posting Date	27–Dec–2019
Official Date	01–May–2020
Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Cyclobenzaprine Hydrochloride monograph. The purpose for the revision is to correct the relative response factors for cyclobenzaprine *N*-oxide and dibenzocycloheptenone in the test for *Organic Impurities*.

The Cyclobenzaprine Hydrochloride Revision Bulletin supersedes the version that is scheduled to become official on May 1, 2020. Please note that Section 3.10 of USP-NF General Notices discusses Early Adoption. For questions regarding compliance, please consult your relevant regulatory authority.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison (301-998-6792 or hrj@usp.org).

Cyclobenzaprine Hydrochloride



$C_{20}H_{21}N \cdot HCl$ 311.85

1-Propanamine, 3-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-*N,N*-dimethyl-, hydrochloride;
N,N-Dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine hydrochloride [6202-23-9].

DEFINITION

Cyclobenzaprine Hydrochloride contains NLT 98.0% and NMT 102.0% of cyclobenzaprine hydrochloride ($C_{20}H_{21}N \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

Change to read:

- **A. ▲Spectroscopic Identification Tests** ⟨197⟩**,** *Infrared Spectroscopy***:** 197M▲ (CN 1-May-2020)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General** ⟨191⟩**,** *Chemical Identification Tests, Chloride*

Sample solution: 20 mg/mL of Cyclobenzaprine Hydrochloride in water
Acceptance criteria: Meets the requirements

ASSAY

- **Procedure**

Mobile phase: Dissolve 2.0 g of ammonium acetate in 350 mL of water. Add 650 mL of methanol, and adjust with 25% ammonium hydroxide to a pH of 8.9.
Standard solution: 0.2 mg/mL of USP Cyclobenzaprine Hydrochloride RS in *Mobile phase*
Sample solution: 0.2 mg/mL of Cyclobenzaprine Hydrochloride in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 226 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of cyclobenzaprine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of cyclobenzaprine hydrochloride ($C_{20}H_{21}N \cdot HCl$) in the portion of Cyclobenzaprine Hydrochloride 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 = concentration of Cyclobenzaprine Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%

Change to read:

- **Organic Impurities**

Buffer: 5.7 g/L of ammonium acetate in water. Adjust with 25% ammonium hydroxide to a pH of 7.2.
Mobile phase: Methanol and *Buffer* (65:35)
System suitability solution: 0.5 mg/mL of USP Cyclobenzaprine Hydrochloride RS and 0.75 µg/mL each of USP Cyclobenzaprine Related Compound A RS and USP Cyclobenzaprine Related Compound B RS in *Mobile phase*
Standard solution: 0.5 µg/mL of USP Cyclobenzaprine Hydrochloride RS in *Mobile phase*
Sample solution: 500 µg/mL of Cyclobenzaprine Hydrochloride in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 240 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 3.5 times the retention time of cyclobenzaprine
System suitability
Samples: *System suitability solution,* and *Standard solution*
[Note—See *Table 1* for relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between cyclobenzaprine related compound A and cyclobenzaprine related compound B, *System suitability solution*
Tailing factor: NMT 2.0 for the cyclobenzaprine peak, *System suitability solution*
Relative standard deviation: NMT 5.0% for cyclobenzaprine, *Standard solution*
Analysis
Samples: *Sample solution* and *Standard solution*
Calculate the percentage of each specified impurity and any individual unspecified impurity in the portion of Cyclobenzaprine Hydrochloride taken:

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

r_U = peak response of each impurity from the *Sample solution*
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 = concentration of Cyclobenzaprine Hydrochloride in the *Sample solution* (µg/mL)
F = relative response factor for each impurity (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%, w/w)
Cyclobenzaprine related compound A	0.51	0.35	0.15
Cyclobenzaprine related compound B	0.57	1.0	0.15
Cyclobenzaprine *N*-oxide[a]	0.74	▲1.0▲ (RB 1-May-2020)	0.15
Dibenzocycloheptenol[b]	0.87	0.45	0.1
Cyclobenzaprine	1.0	—	—
Amitriptyline[c]	1.3	0.48	0.15
Dibenzocycloheptenone[d]	1.6	▲1.4▲ (RB 1-May-2020)	0.15
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] 3-(5*H*-Dibenzo[*a,d*]cycloheptен-5-ylidene)-*N,N*-dimethyl-1-propanamine *N*-oxide.
[b] 5*H*-Dibenzo[*a,d*]cycloheptene-5-ol.
[c] 10,11-Dihydro-*N,N*-dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,\gamma}$,-propylamine.
[d] Dibenzo[*a,d*]cyclohepten-5-one.

SPECIFIC TESTS

- **Loss on Drying** ⟨731⟩
  Analysis: Dry at 105° to constant weight.
  Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.
- **USP Reference Standards** ⟨11⟩
  USP Cyclobenzaprine Hydrochloride RS
  USP Cyclobenzaprine Related Compound A RS
  5-[3-(Dimethylamino)propyl]-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*]cycloheptен-5-ylidene)-*N*-methyl-1-propanamine hydrochloride.
  $C_{19}H_{19}N \cdot HCl$ 297.82