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·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.
  - **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**
    - **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·HCl) in the portion of Tablets taken:
      \[
      \text{Result} = \left( \frac{r_0}{r_3} \right) \times \left( \frac{C_s}{C_l} \right) \times 100
      \]
    - **r$_0$** = peak response from the Sample solution
    - **r$_3$** = peak response from the Sample solution
    - **C$_s$** = concentration of USP Cyclobenzaprine Hydrochloride RS in the Standard solution (mg/mL)
    - **C$_l$** = nominal concentration of cyclobenzaprine hydrochloride in the Sample solution (mg/mL)
  - **Acceptance criteria**: 90.0%–110.0%

**PERFORMANCE TESTS**
- **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**
    - **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·HCl) dissolved:
      \[
      \text{Result} = \left( \frac{A_0}{A_t} \right) \times C_t \times \frac{V}{(1/L)} \times 100
      \]
    - **A$_0$** = absorbance of the Sample solution
    - **A$_t$** = absorbance of the Standard solution
    - **C$_t$** = 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·HCl) is dissolved.
- **Uniformity of Dosage Units (905)**: Meet the requirements

**IMPURITIES**
- **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**
    - **Mode**: LC
    - **Detector**: UV 226 nm
    - **Column**: 4.6-mm × 25-cm; 5-µm packing L7
  - **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·HCl) in the portion of Tablets taken:
      \[
      \text{Result} = \left( \frac{r_0}{r_3} \right) \times \left( \frac{C_s}{C_l} \right) \times 100
      \]
    - **r$_0$** = peak response from the Sample solution
    - **r$_3$** = peak response from the Sample solution
    - **C$_s$** = concentration of USP Cyclobenzaprine Hydrochloride RS in the Standard solution (mg/mL)
    - **C$_l$** = nominal concentration of cyclobenzaprine hydrochloride in the Sample solution (mg/mL)
  - **Acceptance criteria**: 90.0%–110.0%

©2016 The United States Pharmacopeial Convention  All Rights Reserved.
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 in the portion of Tablets taken:

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

- \( r_U \) = peak response of any individual degradation product 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)
- \( C_U \) = nominal concentration of cyclobenzaprine hydrochloride in the Sample solution (µg/mL)

Acceptance criteria: See Table 1.

### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobenzaprine N-oxide</td>
<td>0.74</td>
<td>0.2 (2016)</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>1.3</td>
<td>—</td>
</tr>
<tr>
<td>Dibenzocycloheptone-none</td>
<td>1.6</td>
<td>— (2016)</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* Process impurity included for identification only and not included in the calculation of total degradation products.

** USP Reference Standards (11)

<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP Cyclobenzaprine Hydrochloride RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound A RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound B RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound C RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound D RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound E RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound F RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound G RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound H RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound I RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound J RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound K RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound L RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound M RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound N RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound O RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound P RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound Q RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound R RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound S RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound T RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound U RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound V RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound W RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound X RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound Y RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
<tr>
<td>USP Cyclobenzaprine Related Compound Z RS</td>
<td><img src="image" alt="Structure" /></td>
<td>(ERR 1-Feb-2016)</td>
</tr>
</tbody>
</table>

### ADDITIONAL REQUIREMENTS

- Packaging and Storage: Preserve in well-closed containers. Store at controlled room temperature.

---

©2016 The United States Pharmacopeial Convention All Rights Reserved.