In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Tolterodine Tartrate monograph. The purpose of the revision is to:

- Remove one resolution requirement of “NLT 1.5 between tolterodine dimer and 6-methyl-4-phenylchroman-2-ol” in the test for Organic Impurities.
- Revise the relative retention time for 6-Methyl-4-phenylchroman-2-one in Table 2 from 1.82 to 1.59.

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

Interested parties are invited to contact USP for additional information on this topic and to get involved in future revisions to this monograph. The process for and timing of any future revision to revise the current test or include a new test for Organic impurities will be determined following receipt of sponsor data and consideration by the Expert Committee and USP staff.

The Tolterodine Tartrate Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the First Supplement to USP 41–NF 36.

Should you have any questions, please contact Andrea F. Carney, Associate Scientific Liaison (301-816-8155 or afc@usp.org).
Tolterodine Tartrate

\[ \text{C}_{22}\text{H}_{31}\text{NO} \cdot \text{C}_{4}\text{H}_{6}\text{O}_{6} \] 475.57

(R)-2-[3-[Bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylpheno| (2R,3R)-2,3-dihydroxybutanedioate (1:1) (salt);

(+)-(R)-2-[α-[2-(Diisopropylamino)ethyl]benzyl]-p-cresol l-

DEFINITION
Tolterodine Tartrate contains NLT 97.0% and NMT 103.0% of tolterodine tartrate (C\(_{22}\)H\(_{31}\)NO \cdot C\(_{4}\)H\(_{6}\)O\(_{6}\)), calculated on the as-is basis.

IDENTIFICATION
• A. INFRARED ABSORPTION (197K)
• 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
• PROEDURE
  Mobile phase: Acetonitrile, water, and phosphoric acid (330:670:1)
  Standard solution: 0.35 mg/mL of USP Tolterodine Tartrate RS in Mobile phase.
  Sample solution: 0.35 mg/mL of Tolterodine Tartrate in Mobile phase.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 5 µL

System suitability
Sample: Standard solution
Suitability requirements
Relative standard deviation: NMT 1.0% from six replicate injections

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of tolterodine tartrate
(C\(_{22}\)H\(_{31}\)NO \cdot C\(_{4}\)H\(_{6}\)O\(_{6}\)) in the portion of Tolterodine Tartrate taken:

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

\( r_s \) = peak response from the Sample solution
\( r_U \) = peak response from the Standard solution
\( C_s \) = concentration of USP Tolterodine Tartrate RS in the Standard solution (mg/mL)
\( C_U \) = concentration of Tolterodine Tartrate in the Sample solution (mg/mL)

Acceptance criteria: 97.0%–103.0% on the as-is basis

IMPURITIES
• RESIDUE ON IGNITION (281): NMT 0.1%

Change to read:

• ORGANIC IMPURITIES
Solution A: Acetonitrile, water, and perchloric acid (100: 900: 1.5)
Solution B: Acetonitrile, water, and perchloric acid
Solution C: Acetonitrile

Mobile phase: See Table 1. Return to original conditions, and re-equilibrate the system.

Diluent: Acetonitrile and water (50:50)
System suitability solution: 10 mg/mL of USP Tolterodine System Suitability Mixture RS in Diluent. See Table 2 for relative retention times of the main components of the mixture.

<table>
<thead>
<tr>
<th>Component of USP Tolterodine System Suitability Mixture RS</th>
<th>Relative Retention Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Cresol</td>
<td>0.75</td>
</tr>
<tr>
<td>trans-Cinnamic acid</td>
<td>0.81</td>
</tr>
<tr>
<td>Monoisopropyl tolterodine</td>
<td>0.85</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1.0</td>
</tr>
<tr>
<td>Diol impurity</td>
<td>1.18</td>
</tr>
<tr>
<td>Tolterodine dimer</td>
<td>1.44</td>
</tr>
<tr>
<td>6-Methyl-4-phenylchroman-2-one</td>
<td>1.45</td>
</tr>
<tr>
<td>Diol acetate impurity</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
<th>Solution C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>75</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>47</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>57</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1

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ENANTIOMERIC PURITY

- ADDITIONAL REQUIREMENTS

Monoisopropyl 6-Methyl-4-phenylchroman-2-ol 1.4 1.9 0.25 (phenyl- USP Tolterodine tolterodine 0.88 1.6 0.25

See System suitability

Standard solution: 0.0004 mg/mL of USP Tolterodine Diol acetate impurity;

Chromatographic system

Sample solution: 0.04 mg/mL of Tolterodine Tartrate 6-Methyl-4-phenylchroman-2-ol.

Analysis Column efficiency:

Buffer: Add 0.97 g of tetrabutylammonium C19H25NO 283.41

Mobile phase: Add 0.5 M solution of dibasic sodium C9H8O2 148.16 phosphate dihydrate to a 1000-mL volumetric flask,

System suitability solution: 0.02 mg/mL each of USP C16H18O2 242.32

Sample: System suitability solution

[NOTE—The relative retention times for tolterodine S-enantiomer and tolterodine are 0.9 and 1.0, respectively.]

Table 3

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoisopropyl tolterodine</td>
<td>0.88</td>
<td>1.6</td>
<td>0.25</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6-Methyl-4-phenylchroman-2-ol</td>
<td>1.48</td>
<td>1.9</td>
<td>0.25</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Suitability requirements

Resolution: NLT 1.4 between tolterodine S-enantiomer and tolterodine

Column efficiency: NLT 1500 theoretical plates for tolterodine

Relative standard deviation: NMT 3% for each of tolterodine S-enantiomer and tolterodine

Analysis Samples: Standard solution and Sample solution

Calculate the percentage of tolterodine S-enantiomer in the portion of Tolterodine Tartrate taken:

Result = (rU/rS) × (Cv/Cu) × (1/F) × 100

Diol impurity; 2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol.

Bis[3-(2-hydroxy-5-methylphenyl)-1-phenylpropyl]-4-methylphenyl tartrate.

C7H11NO · C2H9O5 475.57

USP Tolterodine System Suitability Mixture RS

The mixture contains tolterodine tartrate and the following impurities (other impurities may also be present):

p-Cresol.

C6H8O 108.14

trans-Cinnamic acid.

C9H8O2 148.16

Monoisopropyl tolterodine;

(R)-2-[3-(Isopropylamino)-1-phenylpropyl]-4-methylphenol.

C13H22NO 283.41

Diol impurity;

2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol.

C16H15O2 242.32

Tolterodine dimer;

N,N-Bis[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-N-isopropylamine.

C20H25NO5 507.72

6-Methyl-4-phenylchroman-2-ol.

C15H14O2 240.30

Diol acetate impurity;

3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl acetate.

C19H23O2 284.35

6-Methyl-4-phenylchroman-2-one.

C16H17O2 238.29

USP Tolterodine Tartrate RS

SPECIFIC TESTS

- LOSS ON DRYING (731)

Analysis: Dry under vacuum at 100 °C for 2 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

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

- USP REFERENCE STANDARDS (11)

USP Tolterodine S-Enantiomer RS

(S)-2-[3-(Disopropylamino)-1-phenylpropyl]-4-methylphenol tartrate.

C20H23NO · C2H9O5 475.57

USP Tolterodine System Suitability Mixture RS

The mixture contains tolterodine tartrate and the following impurities (other impurities may also be present):

p-Cresol.

C6H8O 108.14

t-trans-Cinnamic acid.

C9H8O2 148.16

Monoisopropyl tolterodine;

(R)-2-[3-(Isopropylamino)-1-phenylpropyl]-4-methylphenol.

C13H22NO 283.41

Diol impurity;

2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol.

C16H15O2 242.32

Tolterodine dimer;

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C15H14O2 240.30

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C19H23O2 284.35

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USP Tolterodine Tartrate RS