Tolterodine Tartrate

Type of Posting	Revision Bulletin
Posting Date	28–Jul–2017
Official Date	01–Aug–2017
Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Substantive error

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

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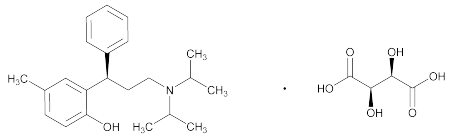
Tolterodine Tartrate



$C_{22}H_{31}NO \cdot C_4H_6O_6$ 475.57

(*R*)-2-[3-[Bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1) (salt);
(+)-(*R*)-2-[α-[2-(Diisopropylamino)ethyl]benzyl]-*p*-cresol L-tartrate (1:1) (salt);
(*R*)-2-[3-(Diisopropylamino)-1-phenylpropyl]-4-methylphenol tartrate [124937-52-6].

DEFINITION

Tolterodine Tartrate contains NLT 97.0% and NMT 103.0% of tolterodine tartrate ($C_{22}H_{31}NO \cdot C_4H_6O_6$), 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

- **Procedure**

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 285 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 ($C_{22}H_{31}NO \cdot C_4H_6O_6$) in the portion of Tolterodine Tartrate 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 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 (500: 500: 1.5)
Solution C: Acetonitrile
Mobile phase: See *Table 1*. Return to original conditions, and re-equilibrate the system.

Table 1

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	75	25	0
5	75	25	0
22	0	100	0
47	0	0	100
57	0	0	100

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 2

Component of USP Tolterodine System Suitability Mixture RS	Relative Retention Time
p-Cresol	0.75
trans-Cinnamic acid	0.81
Monoisopropyl tolterodine	0.88
Tolterodine	1.0
Diol impurity	1.18
Tolterodine dimer[a]	1.44
6-Methyl-4-phenylchroman-2-ol[a]	1.48
Diol acetate impurity	1.54
6-Methyl-4-phenylchroman-2-one	●1.59● (RB 1-Aug-2017)

[a] Undefined stereochemistry.

Standard solution: 0.01 mg/mL of USP Tolterodine Tartrate RS in *Diluent*
Sensitivity solution: 0.005 mg/mL of USP Tolterodine Tartrate RS in *Diluent* from the *Standard solution*
Sample solution: 10 mg/mL of Tolterodine Tartrate in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 65°
Flow rate: 1.0 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Resolution: ●● (RB 1-Aug-2017) NLT 1.5 between diol acetate impurity and 6-methyl-4-phenylchroman-2-one, *System suitability solution*

Relative standard deviation: NMT 3.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tolterodine Tartrate taken:

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

r_U = peak response for each impurity from the *Sample solution*
r_S = peak response of tolterodine 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)
F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. Disregard any peak below 0.05% and any peak eluting at retention times of less than 4 min.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Monoisopropyl tolterodine	0.88	1.6	0.25
Tolterodine	1.0	—	—
6-Methyl-4-phenyl-chroman-2-ol	1.48	1.9	0.25
Any other individual impurity	—	1.0	0.1
Total impurities	—	—	0.5

- **ENANTIOMERIC PURITY**

Buffer: Prepare pH 7.1 buffer as follows. Transfer 21.0 mL of 1 M solution of monobasic sodium phosphate and 53.3 mL of 0.5 M solution of dibasic sodium phosphate dihydrate to a 1000-mL volumetric flask, and dilute with water to volume. Dilute 100.0 mL of this solution with water to 1000.0 mL.
Mobile phase: Add 0.97 g of tetrabutylammonium bromide to a mixture of 930 mL of *Buffer* and 70 mL of isobutyl alcohol.
System suitability solution: 0.02 mg/mL each of USP Tolterodine Tartrate RS and USP Tolterodine *S*-Enantiomer RS in *Mobile phase*
Standard solution: 0.0004 mg/mL of USP Tolterodine *S*-Enantiomer RS in *Mobile phase*
Sample solution: 0.04 mg/mL of Tolterodine Tartrate in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 2-mm × 10-cm; 5-µm packing L41
Flow rate: 0.2 mL/min
Injection volume: 20 µL
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for tolterodine *S*-enantiomer and tolterodine are 0.9 and 1.0, respectively.]
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:

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

r_U = peak response of tolterodine *S*-enantiomer from the *Sample solution*
r_S = peak response of tolterodine *S*-enantiomer from the *Standard solution*
C_S = concentration of USP Tolterodine *S*-Enantiomer RS in the *Standard solution* (mg/mL)
C_U = concentration of Tolterodine Tartrate in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 1.0%

SPECIFIC TESTS

- **LOSS ON DRYING** ⟨731⟩

Analysis: Dry under vacuum at 100° 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-(Diisopropylamino)-1-phenylpropyl]-4-methylphenol tartrate.
$C_{22}H_{31}NO \cdot C_4H_6O_6$ 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.
C_7H_8O 108.14
trans-Cinnamic acid.
$C_9H_8O_2$ 148.16
Monoisopropyl tolterodine;
(*R*)-2-[3-(Isopropylamino)-1-phenylpropyl]-4-methylphenol.
$C_{19}H_{25}NO$ 283.41
Diol impurity;
2-(3-Hydroxy-1-phenylpropyl)-4-methylphenol.
$C_{16}H_{18}O_2$ 242.32
Tolterodine dimer;
N,*N*-Bis[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-*N*-isopropylamine.
$C_{35}H_{41}NO_2$ 507.72
6-Methyl-4-phenylchroman-2-ol.
$C_{16}H_{16}O_2$ 240.30
Diol acetate impurity;
3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl acetate.
$C_{18}H_{20}O_3$ 284.35
6-Methyl-4-phenylchroman-2-one.
$C_{16}H_{14}O_2$ 238.29
USP Tolterodine Tartrate RS