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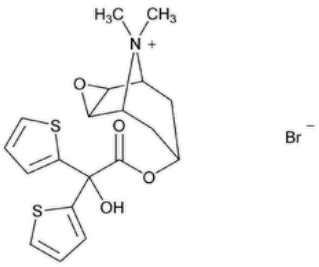
Add the following:

▲Tiotropium Bromide



$C_{19}H_{22}BrNO_4S_2$ 472.41

3-Oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane, 7-[(hydroxydi-2-thienacetyl)oxy]-9,9-dimethyl-, bromide, (1α,2β,4β,5α,7β)-;

(1*R*,2*R*,4*S*,5*S*,7*s*)-7-(2-Hydroxy-2,2-di(thiophen-2-yl)acetoxy)-9,9-dimethyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]nonan-9-ium bromide CAS RN®: 136310-93-5; UNII: XX112XZP0J.

Tiotropium bromide monohydrate

$C_{19}H_{22}BrNO_4S_2 \cdot H_2O$ 490.43 CAS RN®: 411207-31-3; UNII: L64SXO195N.

DEFINITION

Tiotropium Bromide contains NLT 98.0% and NMT 102.0% of tiotropium bromide ($C_{19}H_{22}BrNO_4S_2$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A, 197K, or 197M
- **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, Bromide***

  Sample solution: 10 mg/mL of Tiotropium Bromide in water

  Acceptance criteria: Meets the requirements of test *B* (silver nitrate precipitate test)

ASSAY

- **Procedure**

Protect solutions containing tiotropium bromide from light.

Buffer: 5 g/L of monobasic potassium phosphate and 1 g/L of sodium methanesulfonate in water. Adjust with 1 M phosphoric acid to a pH of 3.0.

Solution A: Acetonitrile, methanol, and *Buffer* (40:10:50)

Mobile phase: *Buffer* and *Solution A* (78:22)

System suitability solution: 0.1 mg/mL each of USP Tiotropium Bromide RS and USP Tiotropium Related Compound C RS in *Solution A*

Standard solution: 0.1 mg/mL of USP Tiotropium Bromide RS in *Solution A*

Sample solution: 0.1 mg/mL of Tiotropium Bromide in *Solution A*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 240 nm

Column: 3.0-mm × 15-cm; 3.5-µm packing L56

Column temperature: 50°

Flow rate: 1.2 mL/min

Injection volume: 5 µL

Run time: NLT 1.6 times the retention time of tiotropium

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between tiotropium and tiotropium related compound C, *System suitability solution*

Tailing factor: NMT 1.8, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of tiotropium bromide ($C_{19}H_{22}BrNO_4S_2$) in the portion of Tiotropium Bromide taken:

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

r_U = peak response of tiotropium from the *Sample solution*

r_S = peak response of tiotropium from the *Standard solution*

C_S = concentration of USP Tiotropium Bromide RS in the *Standard solution* (mg/mL)

C_U = concentration of Tiotropium Bromide in the *Sample solution* (mg/mL)

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

IMPURITIES

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

• **Organic Impurities**

Protect solutions containing tiotropium bromide from light.

Solution A: 5 g/L of monobasic potassium phosphate and 1 g/L of sodium methanesulfonate in water. Adjust with 1 M phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile, methanol, and *Solution A* (40:10:50)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
3	90	10
17	80	20
28	25	75
30	25	75

Standard solution: 20 µg/mL of USP Tiotropium Bromide RS in *Solution B*

Sample solution: 2000 µg/mL of Tiotropium Bromide in *Solution B*

System suitability solution: 2 µg/mL of USP Tiotropium Related Compound C RS in the *Sample solution*

Sensitivity solution: 1 µg/mL of USP Tiotropium Bromide RS in *Solution B*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 240 nm

Column: 3.0-mm × 15-cm; 3.5-µm packing L56

Column temperature: 50°

Flow rate: 1.2 mL/min

Injection volume: 5 µL

System suitability

Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*

Suitability requirements

[NOTE—The relative retention times for tiotropium and tiotropium related compound C are 1.0 and 1.2, respectively.]

Resolution: NLT 2.4 between tiotropium and tiotropium related compound C, *System suitability solution*

Relative standard deviation: NMT 3.0%, *Standard solution*

Tailing factor: NMT 1.5, *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 Tiotropium Bromide 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 tiotropium from the *Standard solution*

C_S = concentration of USP Tiotropium Bromide RS in the *Standard solution* (µg/mL)

C_U = concentration of Tiotropium Bromide in the *Sample solution* (µg/mL)

F = relative response factor for each individual impurity (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Tiotropium related compound A[a]	0.5	2.0	0.10
Tiotropium	1	—	—
Methyl dithienyl glycolate[b]	1.7	2.0	0.10
Dithienyl ketone[c]	1.8	0.28	0.10
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.20

[a] 2-Hydroxy-2,2-di(thiophen-2-yl)acetic acid.

[b] Methyl 2-hydroxy-2,2-di(thiophen-2-yl)acetate.

[c] Di(thiophen-2-yl)methanone.

- **LIMIT OF TIOTROPIUM RELATED COMPOUND G AND TIOTROPIUM RELATED COMPOUND H**

Buffer: 3.9 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.0.

Mobile phase: Acetonitrile and *Buffer* (90:10)

Diluent: 0.01 N hydrochloric acid

Related compound G stock solution: 4 µg/mL of USP Tiotropium Related Compound G RS in *Diluent*

Related compound H stock solution: 4 µg/mL of USP Tiotropium Related Compound H RS in *Diluent*

System suitability solution: 0.04 µg/mL each of USP Tiotropium Related Compound G RS and USP Tiotropium Related Compound H RS from *Related compound G stock solution* and *Related compound H stock solution* in *Diluent*

Sensitivity solution: 0.01 µg/mL each of USP Tiotropium Related Compound G RS and USP Tiotropium Related Compound H RS from *System suitability solution* in *Diluent*

Related compound G standard solution: 0.04 µg/mL of USP Tiotropium Related Compound G RS from *Related compound G stock solution* in *Diluent*

Related compound H standard solution: 0.04 µg/mL of USP Tiotropium Related Compound H RS from *Related compound H stock solution* in *Diluent*

Sample solution: 40 µg/mL of Tiotropium Bromide in *Diluent* prepared as follows. Transfer a suitable amount of Tiotropium Bromide to an appropriate volumetric flask. Add 80% of the flask volume of *Diluent*. Sonicate for NLT 5 min to dissolve and dilute with *Diluent* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: Mass spectrometer

Ionization: Electrospray positive ion. [NOTE—Adjustments to the electrospray source parameters including the probe temperature, cone voltage, and capillary voltage may be necessary to meet *Suitability requirements*.]

Acquisition mode: Selected ion monitoring (SIM) mode with m/z of 170.1 for both tiotropium related compound G and tiotropium related compound H cations

Column: 3.0-mm × 5-cm; 5-µm packing L9

Column temperature: 20°

Flow rate: 0.6 mL/min

Injection volume: 5 µL

Run time: NLT 1.5 times the retention time of tiotropium related compound G

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[NOTE—The relative retention times for tiotropium related compound H and tiotropium related compound G are 0.85 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between tiotropium related compound H and tiotropium related compound G, *System suitability solution*

Relative standard deviation: NMT 10.0% for tiotropium related compound G and tiotropium related compound H, *System suitability solution*

Signal-to-noise ratio: NLT 10 for both tiotropium related compound G and tiotropium related compound H, *Sensitivity solution*

Analysis

Samples: *Related compound G standard solution*, *Related compound H standard solution*, and *Sample solution*

Calculate the percentage of tiotropium related compound G and tiotropium related compound H in the portion of Tiotropium Bromide taken:

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

r_U = peak response of tiotropium related compound G or tiotropium related compound H from the *Sample solution*

r_S = peak response of tiotropium related compound G or tiotropium related compound H from the corresponding *Related compound G standard solution* or *Related compound H standard solution*

C_S = concentration of USP Tiotropium Related Compound G RS in the *Related compound G standard solution* or USP Tiotropium Related Compound H RS in the *Related compound H standard solution* (µg/mL)

C_U = concentration of Tiotropium Bromide in the *Sample solution* (µg/mL)

Acceptance criteria: NMT 0.10% each of tiotropium related compound G and tiotropium related compound H

SPECIFIC TESTS

• **WATER DETERMINATION ⟨921⟩, *Method I, Method Ia*:** NMT 4.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Store in tight containers.

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Tiotropium Bromide RS

USP Tiotropium Related Compound C RS

(1*R*,3*s*,5*S*)-3-[2-Hydroxy-2,2-di(thiophen-2-yl)acetoxy]-8,8-dimethyl-8-azabicyclo[3.2.1]oct-6-en-8-ium bromide.

$C_{19}H_{22}BrNO_3S_2$ 456.41

USP Tiotropium Related Compound G RS

(1*R*,2*R*,4*S*,5*S*,7*s*)-7-Hydroxy-9,9-dimethyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]nonan-9-ium bromide.

$C_9H_{16}BrNO_2$ 250.14

USP Tiotropium Related Compound H RS

(2*RS*,3a*SR*,5*RS*,6*RS*,6a*RS*)-6-Hydroxy-4,4-dimethylhexahydro-2*H*-2,5-methanofuro[3,2-*b*]pyrrol-4-ium bromide (may be a mixture of two stereoisomers).

$C_9H_{16}BrNO_2$ 250.14▲ (USP 1-Dec-2022)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
TIOTROPIUM BROMIDE	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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