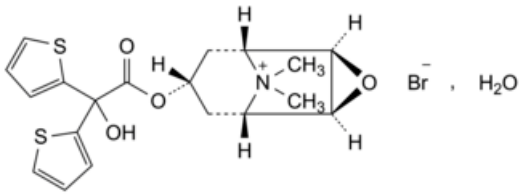
Edition: BP 2025 (Ph. Eur. 11.6 update)

Tiotropium Bromide Monohydrate

General Notices

(Ph. Eur. monograph 2420)



$C_{19}H_{22}BrNO_4S_2,H_2O$ 490.4 *411207-31-3*

Action and use

Anticholinergic (antimuscarinic) bronchodilator.

Ph Eur

DEFINITION

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

Content

98.5 per cent to 101.5 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish-white powder or crystals.

Solubility

Sparingly soluble in water, soluble in methanol, practically insoluble in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *tiotropium bromide monohydrate CRS*.

B. It gives reaction (a) of bromides (2.3.1).

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution Y_6 (2.2.2, *Method II*).

Dissolve 0.2 g in *water R* and dilute to 20 mL with the same solvent.

Impurities G and H

Thin-layer chromatography (2.2.27). *Prepare the solutions immediately before use.*

Solvent mixture Dilute 1 volume of a 103 g/L solution of *hydrochloric acid R* to 100 volumes with *methanol R*.

Test solution Dissolve 0.40 g of the substance to be examined in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *tiotropium impurity mixture CRS* (containing impurities G and H) in 1.0 mL of the solvent mixture.

Reference solution (b) Mix 0.1 mL of the test solution with 0.1 mL of reference solution (a).

Plate *TLC silica gel F_{254} plate R* (2-10 µm).

Mobile phase *water R*, *anhydrous formic acid R*, *acetonitrile R*, *methylene chloride R* (10:15:35:50 *V/V/V/V*).

Application 10 µL of the test solution and reference solution (a), and 20 µL of reference solution (b).

Development Over 2/3 of the plate.

Drying In air.

Detection Expose to iodine vapour until the spots are clearly visible (about 15 min); remove the plate and examine immediately.

Retardation factors Impurity G = about 0.33; impurity H = about 0.38; tiotropium = about 0.64.

System suitability Reference solution (b):

— the chromatogram shows 3 clearly separated spots.

Limits:

— *impurity G*: any spot due to impurity G is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.1 per cent);

— *impurity H*: any spot due to impurity H is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.1 per cent).

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions protected from light.*

Test solution Dissolve 50.0 mg of the substance to be examined in mobile phase B and dilute to 25.0 mL with mobile phase B.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase B. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase B.

Reference solution (b) Dissolve 4 mg of *tiotropium for system suitability 1 CRS* (containing impurity C) in 2.0 mL of mobile phase B.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: *propylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of *sodium methanesulfonate R* and 5.0 g of *potassium dihydrogen phosphate R* in about 980 mL of *water R*, adjust to pH 3.0 with *dilute phosphoric acid R* and dilute to 1000 mL with *water R*;

— *mobile phase B*: *methanol R1*, *acetonitrile for chromatography R*, mobile phase A (10:40:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	90	10
3 - 17	90 → 80	10 → 20
17 - 28	80 → 25	20 → 75
28 - 30	25	75

Flow rate 1.2 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 5 µL.

Identification of impurities Use the chromatogram supplied with *tiotropium for system suitability 1 CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to tiotropium (retention time = about 15 min): impurity C = about 1.2.

System suitability Reference solution (b):

— *resolution*: minimum 2.4 between the peaks due to tiotropium and impurity C.

Limits:

— *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

2.5 per cent to 4.0 per cent, determined on 0.300 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

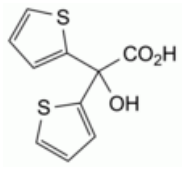
Dissolve 0.35 g in 100 mL of *water R*. Add 10 mL of *dilute nitric acid R2*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 47.24 mg of $C_{19}H_{22}BrNO_4S_2$.

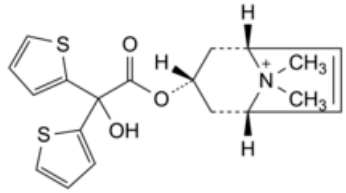
IMPURITIES

Specified impurities G, H.

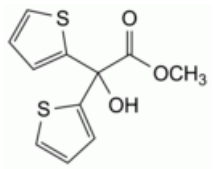
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, C, E, F.



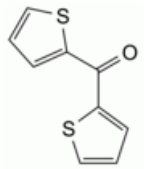
A. hydroxy[di(thiophen-2-yl)]acetic acid,



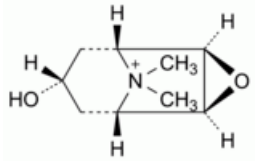
C. (1*R*,3*s*,5*S*)-3-[[hydroxy[di(thiophen-2-yl)]acetyl]oxy]-8,8-dimethyl-8-azabicyclo[3.2.1]oct-6-en-8-ium,



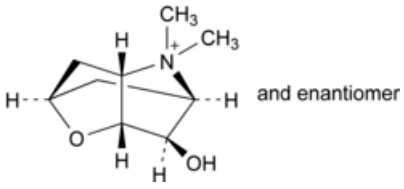
E. methyl hydroxy[di(thiophen-2-yl)]acetate,



F. di(thiophen-2-yl)methanone,



G. (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,



and enantiomer

H. (1*s*,3*RS*,4*RS*,5*RS*,7*SR*)-4-hydroxy-6,6-dimethyl-2-oxa-6-azatricyclo[3.3.1.0^{3,7}]nonan-6-ium.

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