

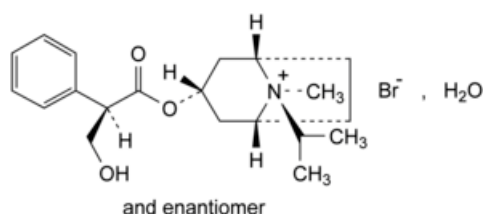


Edition: BP 2025 (Ph. Eur. 11.6 update)

## Ipratropium Bromide

### [General Notices](#)

(Ph. Eur. monograph 0919)



$C_{20}H_{30}BrNO_3 \cdot H_2O$  430.4 66985-17-9

### Action and use

Anticholinergic (antimuscarinic) bronchodilator.

### Preparations

[Ipratropium Nebuliser Solution](#)

[Ipratropium Pressurised Inhalation](#)

Ph Eur

## DEFINITION

(1*R*,3*r*,5*S*,8*r*)-3-[[[(2*RS*)-3-Hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide monohydrate.

### Content

99.0 per cent to 100.5 per cent (anhydrous substance).

## CHARACTERS

### Appearance

White or almost white, crystalline powder.

### Solubility

Soluble in water, freely soluble in methanol, slightly soluble in ethanol (96 per cent).

**mp**

About 230 °C, with decomposition.

## IDENTIFICATION

*First identification:* A, E.

*Second identification:* B, C, D, E.

A. Infrared absorption spectrophotometry ([2.2.24](#)).

*Comparison* [ipratropium bromide CRS](#).

B. Examine the chromatograms obtained in the test for impurity A.

*Results* The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. To 5 mL of solution S (see Tests), add 2 mL of [dilute sodium hydroxide solution R](#). No precipitate is formed.

D. To about 1 mg add 0.2 mL of [nitric acid R](#) and evaporate to dryness on a water-bath. Dissolve the residue in 2 mL of [acetone R](#) and add 0.1 mL of a 30 g/L solution of [potassium hydroxide R](#) in [methanol R](#). A violet colour develops.

E. It gives reaction (a) of bromides ([2.3.1](#)).

## TESTS

### Solution S

Dissolve 0.50 g in [carbon dioxide-free water R](#) and dilute to 50.0 mL with the same solvent.

### Appearance of solution

Solution S is clear ([2.2.1](#)) and not more intensely coloured than reference solution GY<sub>7</sub> ([2.2.2, Method II](#)).

### pH ([2.2.3](#))

5.0 to 7.5 for solution S.

### Impurity A

Thin-layer chromatography ([2.2.27](#)).

*Test solution* Dissolve 20 mg of the substance to be examined in [methanol R](#) and dilute to 1.0 mL with the same solvent.

*Reference solution (a)* Dissolve 20 mg of [ipratropium bromide CRS](#) in [methanol R](#) and dilute to 1.0 mL with the same solvent.

*Reference solution (b)* Dissolve 20 mg of [methyldatropine bromide CRS](#) in 1.0 mL of reference solution (a).

*Reference solution (c)* Dissolve 5 mg of [ipratropium impurity A CRS](#) in 100.0 mL of [methanol R](#). Dilute 2.0 mL of the solution to 5.0 mL with [methanol R](#).

*Plate* [TLC silica gel plate R](#) (2-10 µm).

*Mobile phase* [anhydrous formic acid R](#), [water R](#), [ethanol \(96 per cent\) R](#), [methylene chloride R](#) (1:3:18:18 V/V/V/V).

*Application* 1 µL.

*Development* Over a path of 6 cm.

*Drying* At 60 °C for 15 min.

**Detection** Spray with [potassium iodobismuthate solution R5](#), allow the plate to dry in air, spray with a 50 g/L solution of [sodium nitrite R](#) and protect immediately with a sheet of glass.

**System suitability** The chromatogram obtained with reference solution (b) shows 2 clearly separated principal spots.

**Limit:**

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

## Related substances

Liquid chromatography ([2.2.29](#)).

**Test solution** Dissolve 0.200 g of the substance to be examined in the mobile phase and dilute to 20.0 mL with the mobile phase.

**Reference solution (a)** Dissolve 10.0 mg of [ipratropium bromide CRS](#) in the mobile phase and dilute to 20.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 50.0 mL with the mobile phase.

**Reference solution (b)** Dissolve 5 mg of [ipratropium bromide CRS](#) and 5 mg of [ipratropium impurity B CRS](#) in 1 mL of [methanol R](#) and dilute to 25.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 20.0 mL with the mobile phase.

**Column:**

— **size:**  $l = 0.15$  m,  $\varnothing = 3.9$  mm;

— **stationary phase:** [octadecylsilyl silica gel for chromatography R](#) (5  $\mu$ m);

— **temperature:** 30 °C.

**Mobile phase** Dissolve 12.4 g of [sodium dihydrogen phosphate R](#) and 1.7 g of [tetrapropylammonium chloride R](#) in 870 mL of [water for chromatography R](#); adjust to pH 5.5 with a 180 g/L solution of [disodium hydrogen phosphate dodecahydrate R](#) and add 130 mL of [methanol R1](#).

**Flow rate** 1.5 mL/min.

**Detection** Spectrophotometer at 220 nm.

**Injection** 5  $\mu$ L.

**Run time** 6 times the retention time of ipratropium.

**Relative retention** With reference to ipratropium (retention time = about 4.9 min): impurity C = about 0.7; impurity B = about 1.2; impurity D = about 1.8; impurity E = about 2.3; impurity F = about 5.1.

**System suitability** Reference solution (b):

— **resolution:** minimum 3.0 between the peaks due to impurity B and ipratropium;

— **symmetry factor:** maximum 2.5 for the principal peak.

**Limits:**

— **correction factors:** for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.3; impurity D = 0.2; impurity F = 0.5;

— **impurity D:** not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent);

— **impurities B, C:** for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent);

— **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 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.25 per cent);

— **disregard limit:** one-third of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.03 per cent); disregard the peak due to the bromide ion.

**Water** (2.5.12)

3.9 per cent to 4.4 per cent, determined on 0.50 g.

**Sulfated ash** (2.4.14)

Maximum 0.1 per cent, determined on 1.0 g.

**ASSAY**

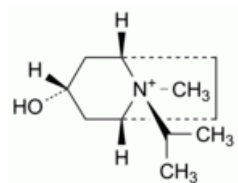
Dissolve 0.350 g in 50 mL of [water R](#) and add 3 mL of [dilute nitric acid R](#). Titrate with [0.1 M silver nitrate](#), determining the end-point potentiometrically (2.2.20).

1 mL of [0.1 M silver nitrate](#) is equivalent to 41.24 mg of  $C_{20}H_{30}BrNO_3$ .

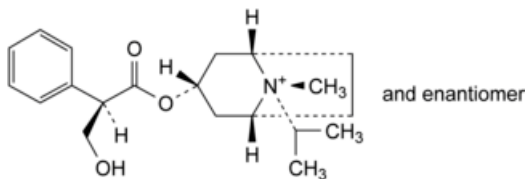
**IMPURITIES**

*Specified impurities* A, B, C, D.

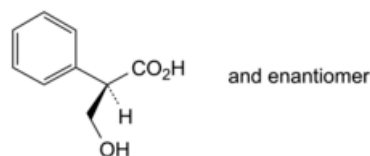
*Other detectable impurities* (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph [Substances for pharmaceutical 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](#)) E, F.



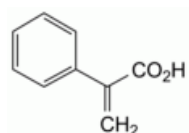
A. (1R,3r,5S,8r)-3-hydroxy-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,



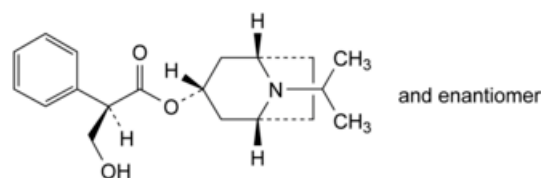
B. (1R,3r,5S,8s)-3-[[2RS)-3-hydroxy-2-phenylpropanoyl]oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane,



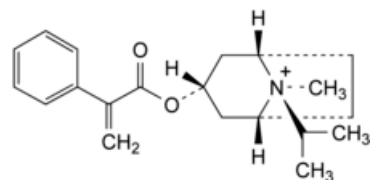
C. (2RS)-3-hydroxy-2-phenylpropanoic acid (DL-tropic acid),



D. 2-phenylpropenoic acid (atropic acid),



E. (1*R*,3*r*,5*S*)-8-(1-methylethyl)-8-azabicyclo[3.2.1]oct-3-yl (2*RS*)-3-hydroxy-2-phenylpropanoate,



F. (1*R*,3*r*,5*S*,8*r*)-8-methyl-8-(1-methylethyl)-3-[(2-phenylpropenoyl)oxy]-8-azoniabicyclo[3.2.1]octane.

Ph Eur