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

Ipratropium Pressurised Inhalation, Solution

General Notices

Ipratropium Pressurised Inhalation

Action and use

Anticholinergic (antimuscarinic) bronchodilator.

DEFINITION

Ipratropium Pressurised Inhalation, Solution is a solution of Ipratropium Bromide in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of ipratropium bromide, $C_{20}H_{30}NO_3Br,H_2O$

85.0 to 115.0% of the stated delivered dose (ex-actuator).

IDENTIFICATION

A. In the test for Impurity A, the principal spot in the chromatogram obtained with solution (2) corresponds to that in the chromatogram obtained with solution (4).
B. In the Uniformity of delivered dose, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to ipratropium bromide in the chromatogram obtained with solution (2).

TESTS

Impurity A

Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.

Solution A To one volume of *potassium iodobismuthate solution*, add 2 volumes of *glacial acetic acid* and 10 volumes of *water*.

(1) Place three containers into a freezer for about 20 minutes and punch a small hole in the can wall of each frozen container, allow the propellant to evaporate for about 1 minute and open the containers. Evaporate the contents under a stream of nitrogen and dissolve the residues in sufficient 0.01M *hydrochloric acid* to make a solution expected to contain 0.6% w/v of ipratropium bromide.
(2) Dilute 1 volume of solution (1) to 50 volumes with 0.01M *hydrochloric acid*.
(3) 0.08% w/v of *8s-isopropyl-3β-hydroxytropanium bromide BPCRS* (impurity A) in 0.01M *hydrochloric acid*.
(4) 0.08% w/v of *ipratropium bromide BPCRS* in 0.01M *hydrochloric acid*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 15 µL of each solution.
(d) Develop the plate to 6 cm.
(e) After removal of the plate, dry it in a current of warm air for about 30 minutes. Spray the plate with Solution A, allow to dry briefly, spray with *sodium nitrite solution* and immediately examine the plate.

MOBILE PHASE

5 volumes of *water*, 8 volumes of *formic acid*, 28 volumes of *methanol* and 70 volumes of *dichloromethane*.

LIMITS

In the chromatogram obtained with solution (1):

any spot corresponding to impurity A is not more intense than the spot in the chromatogram obtained with solution (2) (2%).

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A *Water*, adjusted to pH 2.6 with *orthophosphoric acid*.

(1) Empty the contents of one container into a 50 mL-volumetric flask, wash the container with 5 mL of solution A and add the washing to the flask. Make up to volume with solution A. Dilute, if necessary, with sufficient solution A to make a solution containing 0.04% w/v of ipratropium bromide.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) 0.0002% w/v of *ipratropium bromide impurity D BPCRS* and 0.0002% w/v of *ipratropium bromide BPCRS* in solution A.
(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 1.3 mL per minute.
(d) Use a column temperature of 45°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 50 µL of each solution.
(g) Allow the chromatography to proceed for six times the retention time of ipratropium bromide.

MOBILE PHASE

185 volumes of *acetonitrile R1* and 815 volumes of a 0.16% w/v of *sodium butanesulfonate*, adjusted to pH 2.6 with *orthophosphoric acid.*

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to ipratropium bromide (retention time about 4 minutes) are: for impurity C, about 0.7; impurity D, about 3.5 and impurity F, about 5.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peak due to ipratropium bromide and the peak due to impurity D, is not less than 4.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any other *secondary peak* is not greater than half the area of the corresponding peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of delivered dose

Complies with the requirements stated under Pressurised Metered-dose Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A *water*, adjusted to pH 2.6 with *orthophosphoric acid*.

(1) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient solution A to produce a solution containing the equivalent of 0.0002% w/v of ipratropium bromide.
(2) 0.0002% w/v of *ipratropium bromide BPCRS* in solution A.
(3) Mix 1 volume of solution (2) with 1 volume of 0.0002% w/v of *ipratropium bromide impurity D BPCRS* in solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *base-deactivated octadecylsilyl silica gel for chromatography* (5 µm) (Zorbax SB-C18 is suitable).
(b) Use isocratic elution using the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use a column temperature of 35°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 100 µL of each solution.
(g) Allow the chromatography to proceed for 1.6 times the retention time of ipratropium bromide.

MOBILE PHASE

225 volumes of *acetonitrile* and 775 volumes of a 0.209% w/v solution of *sodium heptanesulfonate*, and adjusted to pH 2.6 with *orthophosphoric acid*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peak due to ipratropium bromide and the peak due to impurity D, is not less than 4.0.

DETERMINATION OF CONTENT

Calculate the content of ipratropium bromide $C_{20}H_{30}BrNO_3,H_2O$ per delivered dose using the declared content of $C_{20}H_{30}BrNO_3,H_2O$ in *ipratropium bromide BPCRS*. Repeat the procedure as described under *Pressurised Metered-dose Preparations for Inhalation, Uniformity of Delivered Dose*.

ASSAY

Use the average of the individual results obtained in the test for Uniformity of delivered dose.

LABELLING

The label states the content of active ingredient in terms of the equivalent delivered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, C, D and F listed under Ipratropium Bromide.