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Ipratropium Pressurised Inhalation, Solution

General Notices

Ipratropium Pressurised Inhalation

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 2
Contact Details	helen.corns@mhra.gov.uk rachael.feltham@mhra.gov.uk sophie.cherrington@mhra.gov.uk bpcom@mhra.gov.uk
Deadline for Comment	30th September 2026
Target Publication Date (subject to change)	BP 2028
Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **Content** Revised expression of content. Please note that this amendment does not require a labeling change for established products. Removal of "ex actuator" following PCN decision. **Identification** HPLC-DAD method introduced, harmonised with Uniformity of delivered dose. **Uniformity of delivered dose** Stoichiometric conversion factor included in determination of content. **Impurity A** Test removed, controlled using impurity C. **Related substances** Test amended to accommodate lower strength products and quantitative limits introduced. **Labelling** Included that the active ingredient is stated in terms of equivalent amount of anhydrous ipratropium bromide.

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 anhydrous ipratropium bromide, $C_{20}H_{30}NO_3Br$

85.0 to 115.0% of the stated delivered dose.

IDENTIFICATION

In the Uniformity of delivered dose, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

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 anhydrous ipratropium bromide.
(2) 0.000209% w/v of *ipratropium bromide BPCRS* .
(3) Mix 1 volume of solution (2) with 1 volume of 0.0002% w/v of *ipratropium bromide impurity D BPCRS* .

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.

MOBILE PHASE

225 volumes of *acetonitrile* and 775 volumes of a 0.209% w/v solution of *sodium heptanesulfonate*. Adjust the pH of the mixture to 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 and impurity D is not less than 4.0.

DETERMINATION OF CONTENT

Calculate the content of anhydrous ipratropium bromide, $C_{20}H_{30}BrNO_3$, per delivered dose using the declared content of $C_{20}H_{30}BrNO_3,H_2O$ in *ipratropium bromide BPCRS*. Each mg of $C_{20}H_{30}BrNO_3,H_2O$ is equivalent to 0.9581 mg of $C_{20}H_{30}BrNO_3$. Repeat the procedure as described under *Pressurised Metered-dose Preparations for Inhalation, Uniformity of Delivered Dose*.

Related substances

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

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

(1) Prepare the sample in an appropriate manner and dissolve a quantity of the pressurised inhalation in sufficient solution B to produce a solution containing the equivalent of 0.04% w/v of anhydrous ipratropium bromide.
(2) Dilute 1 volume of solution (1) to 100 volumes.
(3) 0.0002% w/v of *ipratropium bromide impurity D BPCRS* and 0.0002% w/v of *ipratropium bromide BPCRS*.
(4) Dilute 1 volume of solution (2) to 10 volumes.

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.

MOBILE PHASE

185 volumes of *acetonitrile R1* and 815 volumes of a 0.16% w/v of *sodium butanesulfonate*. Adjust the pH of the mixture 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 and impurity D is not less than 4.0.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of anhydrous ipratropium bromide in solution (2).

For the reporting threshold, use the concentration of anhydrous ipratropium bromide in solution (4).

For peak identification, use solution (3).

Ipratropium retention time: about 4 minutes.

Relative retentions: impurity C, about 0.7; impurity D, about 3.5 and impurity F, about 5.0.

LIMITS

— unspecified impurities: for each impurity, not more than 0.5%;

— total impurities: not more than 1.5%;

— reporting threshold: 0.1%.

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.

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous ipratropium bromide.

IMPURITIES

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