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Budesonide Pressurised Inhalation

General Notices

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

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Notes	Revised monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. Related substances Threshold amended.

Action and use

Glucocorticoid.

DEFINITION

Budesonide Pressurised Inhalation is a suspension of Budesonide 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 budesonide, C₂₅H₃₄O₆

80.0 to 120.0% of the amount stated to be delivered by actuation of the valve.

IDENTIFICATION

- A. Dilute a quantity of the pressurised inhalation with sufficient [water](#) to produce a solution containing 0.002% w/v of Budesonide and filter. The [light absorption](#) of the resulting solution, [Appendix II B](#), in the range 200 nm to 350 nm exhibits a maximum only at 247 nm.
- B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions, protected from light.

Solvent A 34 volumes of [acetonitrile](#) and 66 volumes of [phosphate buffer solution pH 3.2](#).

- (1) Freeze the pressurised container and carefully open the canister. Dissolve a quantity of the frozen contents containing 2 mg of Budesonide in 3.4 mL of [acetonitrile](#). Mix with the aid of ultrasound and add sufficient [phosphate buffer solution pH 3.2](#) to produce 10 mL and filter.
- (2) Dilute 1 volume of solution (1) to 200 volumes with solvent A.
- (3) Dilute 1 volume of solution (2) to 5 volumes with solvent A.

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (15 cm × 4.6 mm) packed with [end-capped octadecylsilyl silica gel for chromatography](#) (3 µm) (Spherisorb ODS2 is suitable).
- (b) Use gradient elution and the mobile phase described below.
- (c) Use a flow rate of 1 mL per minute.
- (d) Use a column temperature of 50°.
- (e) Use a detection wavelength of 240 nm.
- (f) Inject 100 µL of each solution.

MOBILE PHASE

Mobile phase A 2 volumes of [ethanol](#), 34 volumes of [acetonitrile](#) and 66 volumes of [phosphate buffer solution pH 3.2](#).

Mobile phase B Equal volumes of [acetonitrile](#) and [phosphate buffer solution pH 3.2](#).

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-38	100	0	isocratic
38-50	100→0	0→100	linear gradient
50-60	0	100	isocratic
60-61	0→100	100→0	linear gradient
61-70	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions the retention time relative to budesonide epimer B (retention time about 17 minutes) is epimer A, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless:

in the chromatogram obtained with solution (2), the [resolution](#) between the peaks due to epimer B and epimer A is at least 1.5;

in the chromatogram obtained with solution (3), the [signal-to-noise ratio](#) of each of the peaks due to epimer A and epimer B is at least 10.

LIMITS

In the chromatogram obtained with solution (1):

the area of any [secondary peak](#) is not greater than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of any [secondary peaks](#) is not greater than 3 times the sum of the areas of the epimer peaks in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than the sum of the areas of the epimer peaks in the chromatogram obtained with solution (3) (0.1%).

Epimer A

In the chromatogram obtained with solution (1), as described under Assay, the content of epimer A (second peak) is 40.0% to 51.0% of the sum of the areas of the two epimer peaks of budesonide.

ASSAY

Protect the solutions from light.

Determine the content of active ingredient delivered by the first 10 successive combined actuations of the valve after priming. Carry out the procedure for Content of active ingredient delivered by actuation of the valve described under [Appendix XII C](#), beginning at the words 'Remove the pressurised container from the actuator ...' and ending at the words '... to the volume specified in the monograph', using 32 mL of [acetonitrile](#) in the vessel. Transfer the combined solution and washings obtained from the set of 10 combined actuations to a flask so that, on dilution to volume with appropriate amounts of [acetonitrile](#) and [phosphate buffer solution pH 3.2](#), the final solution contains 0.002% w/v of Budesonide in solvent A, as described under Related substances (solution A). Determine the content of active ingredient in the 10 combined actuations using the following method of analysis.

Carry out the method for [liquid chromatography](#), [Appendix III D](#), using the following solutions.

- (1) Solution A.
- (2) 0.002% w/v of [budesonide BPCRS](#) in solvent A.

CHROMATOGRAPHIC CONDITIONS

- (a) Use a stainless steel column (15 cm × 4.6 mm) packed with [end-capped octadecylsilyl silica gel for chromatography](#) (3 µm) (Spherisorb ODS2 is suitable).
- (b) Use isocratic elution and the mobile phase described below.
- (c) Use a flow rate of 1.5 mL per minute.
- (d) Use a column temperature of 50°.
- (e) Use a detection wavelength of 240 nm.
- (f) Inject 20 µL of each solution.

MOBILE PHASE

2 volumes of [ethanol](#), 34 volumes of [acetonitrile](#) and 66 volumes of [phosphate buffer solution pH 3.2](#).

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (2), the [resolution](#) between the peaks due to epimer B and epimer A is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of $C_{25}H_{34}O_6$ in the pressurised inhalation from the sum of the areas of the two budesonide epimer peaks and using the declared content of $C_{25}H_{34}O_6$ in [budesonide BPCRS](#).

Determine the content of active ingredient a second and third time by repeating the procedure on the middle 10 and on the last 10 successive combined actuations of the valve, as estimated from the number of deliveries available from the container as stated on the label. For each of the three determinations the average content of $C_{25}H_{34}O_6$ delivered by a single actuation of the valve is within the limits stated under Content of budesonide.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Budesonide.