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Notes:	

Fluticasone and Salmeterol Pressurised Inhalation, Suspension

Fluticasone Preparations

Action and use
Glucocorticoid and beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Fluticasone and Salmeterol Pressurised Inhalation, Suspension is a suspension of Fluticasone Propionate and Salmeterol Xinafoate 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.

Content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$
75.0 to 101.0% of the stated amount.

Content of salmeterol, $C_{25}H_{37}NO_4$
71.5 to 96.5% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 210 to 300 nm of solution (2) obtained in the test for Uniformity of delivered dose closely resembles that of a solution containing 0.000025% w/v of *salmeterol xinafoate BPCRS* and an appropriate concentration of *fluticasone propionate BPCRS*, depending on the strength of the product, in a mixture of *methanol (70%)*.

B. In the test for Uniformity of delivered dose, the chromatogram obtained with solution (1) shows a peak with the same retention time as the peak due to fluticasone propionate in the chromatogram obtained with solution (3).

C. In the test for Uniformity of delivered dose, the chromatogram obtained with solution (2) shows a peak with the same retention time as the peak due to salmeterol in the chromatogram obtained with solution (3).

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.

(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 *methanol (70%)* to produce a solution containing 0.000125% w/v of Fluticasone Propionate.

(2) 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 *methanol (70%)* to produce a solution containing the equivalent of 0.000025% w/v of salmeterol.

(3) 0.000125% w/v of *fluticasone propionate BPCRS* and 0.000036% w/v of *salmeterol xinafoate BPCRS* in *methanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (20 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Hypersil BDS C18 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 40°.

(e) Use a detection wavelength of 239 nm and a fluorimetric detector with an excitation wavelength of 225 nm and an emission wavelength of 305 nm.

(f) Inject 200 µL of each solution.

MOBILE PHASE

30 volumes of *acetonitrile*, 30 volumes of *methanol* and 40 volumes of a solution containing 0.2M *ammonium acetate* and 0.5% w/v of *tetrabutylammonium hydrogen sulfate* in *water*.

When the chromatograms are recorded under the prescribed conditions the retention time of salmeterol is about 4 minutes and the retention time of fluticasone propionate is about 9 minutes.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between salmeterol and fluticasone propionate is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of fluticasone propionate, $C_{25}H_{31}F_3O_5S$, per delivered dose using the declared content of $C_{25}H_{31}F_3O_5S$, in *fluticasone propionate BPCRS* at 239 nm.

Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{25}H_{37}NO_4$ in *salmeterol xinafoate BPCRS* using fluorimetric detection.

Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

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Related substances

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

Solution A 0.5 volumes of *orthophosphoric acid*, 300 volumes of *water* and 700 volumes of *methanol*.

(1) Dissolve with the aid of ultrasound, a quantity of the suspension containing 2 mg of Fluticasone Propionate in 7 mL of 0.05% v/v of *orthophosphoric acid* in *methanol*. Add 3 mL of *water* and mix for a further 5 minutes.

(2) Dissolve with the aid of ultrasound, a quantity of the suspension containing the equivalent of 1 mg of salmeterol in 7 mL of 0.05% v/v of *orthophosphoric acid* in *methanol*. Add 3 mL of *water* and mix for a further 5 minutes.

(3) Dilute 2 volumes of solution (1) to 100 volumes with solution A. Further dilute 1 volume of the resulting solution to 10 volumes with solution A.

(4) Dilute 2 volumes of solution (2) to 100 volumes with solution A. Further dilute 1 volume of the resulting solution to 10 volumes with solution A.

(5) 0.005% w/v of *fluticasone propionate BPCRS* and 0.00002% w/v of *fluticasone S-methyl BPCRS* (fluticasone propionate impurity D) in *methanol (70%)*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel* (5 µm) (Inertsil ODS2 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.

(d) Use a column temperature of 35°.

(e) Use a detection wavelength of 228 nm.

(f) Inject 50 µL of each solution.

MOBILE PHASE

Mobile phase A 30 volumes of *acetonitrile* and 70 volumes of 0.05M *ammonium dihydrogen orthophosphate*, previously adjusted to pH 2.9 with 10% v/v of *orthophosphoric acid*.

Mobile phase B 22 volumes of 0.05M *ammonium dihydrogen orthophosphate*, previously adjusted to pH 2.9 with 10% v/v of *orthophosphoric acid* and 78 volumes of *acetonitrile*.

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When the chromatograms are recorded under the prescribed conditions the retentions relative to fluticasone propionate (retention time about 37 minutes) are:

Name	Relative retention time
Salmeterol Xinafoate impurity A	0.14
Salmeterol Xinafoate impurity B	0.25
Salmeterol Xinafoate impurity C	0.32
Salmeterol Xinafoate impurity E	0.37
Fluticasone Propionate impurity 1	0.38
Salmeterol	0.41
Xinafoate	0.50
Salmeterol Xinafoate impurity 5	0.55
Fluticasone Propionate impurity A	0.59
Fluticasone Propionate impurity 2	0.67
Salmeterol Xinafoate impurity G	0.71
Fluticasone Propionate impurity 3	0.87
Fluticasone Propionate impurity C	0.89
Fluticasone Propionate impurity 4	0.90
Fluticasone Propionate impurity D	0.97
Fluticasone Propionate impurity E	1.05
Fluticasone Propionate impurity F	1.08
Fluticasone Propionate impurity G	1.09
Fluticasone Propionate impurity H	1.48

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (5), the *resolution* between fluticasone propionate impurity D and fluticasone propionate is at least 1.5.

LIMITS

For fluticasone propionate In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity D and any peak corresponding to impurity G is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.3%);

the area of any other *secondary peak* is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (3) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (3) (1.2%).

Disregard any peak with an area less than half the area of the peak due to fluticasone in the chromatogram obtained with solution (3) (0.1%).

For salmeterol In the chromatogram obtained with solution (2):

the area of any *secondary peak* is not greater than 2.5 times the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (0.5%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (1.0%).

Disregard any peak with an area less than half the area of the peak due to salmeterol in the chromatogram obtained with solution (4) (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 fluticasone propionate and salmeterol in terms of the equivalent metered dose.

IMPURITIES

The impurities limited by the requirements of this monograph include:

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A, C, D, E, F, G and H listed under Fluticasone Propionate
and A, B, C, E and G listed under Salmeterol Xinafoate.

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