Fluticasone and Salmeterol Inhalation Powder, metered-dose

General Notices

Fluticasone and Salmeterol Inhalation Powder, pre-dispensed

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

<table>
<thead>
<tr>
<th>EAG MC3</th>
<th>Medicinal Chemicals 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Details</td>
<td><a href="mailto:adrian.evans@mhra.gov.uk">adrian.evans@mhra.gov.uk</a></td>
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<tr>
<td>Deadline for Comment</td>
<td>30th June 2020</td>
</tr>
<tr>
<td>Target Publication Date (subject to change)</td>
<td>BP 2022</td>
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<tr>
<td>Notes:</td>
<td>Revised monograph</td>
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</tbody>
</table>

Action and use

Glucocorticoid and beta₂-adrenoceptor agonist; bronchodilator.

DEFINITION

Fluticasone and Salmeterol Inhalation Powder, metered-dose consists of Fluticasone Propionate and Salmeterol Xinafoate in microfine powder either alone or combined with a carrier 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
Fluticasone and Salmeterol Inhalation Powder, metered-dose

compliant authority.

**Content of fluticasone propionate, C\textsubscript{25}H\textsubscript{31}F\textsubscript{3}O\textsubscript{5}S**

85.0 to 115.0% of the stated amount.

**Content of salmeterol, C\textsubscript{25}H\textsubscript{37}NO\textsubscript{4}**

85.0 to 115.0% 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 0.00005% w/v of salmeterol xinafoate BPCRS and an appropriate concentration of fluticasone propionate BPCRS in methanol (70%).

B. In the Assay, 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), and 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 Inhalation Powders 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 Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient methanol (70%) to produce a solution containing 0.00025% w/v of Fluticasone Propionate.

2. Collect single doses of the preparation being examined using the procedure described under Inhalation Powders, Uniformity of delivered dose and dissolve the collected dose in sufficient methanol (70%) to produce a solution containing the equivalent of 0.00005% w/v of salmeterol.

3. 0.00025% w/v of fluticasone propionate BPCRS and 0.00007% 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 100 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 the peaks due to salmeterol and fluticasone propionate is at least 6.0.

DETERMINATION OF CONTENT

Calculate the content of fluticasone propionate, C_{25}H_{31}F_{3}O_{5}S, per delivered dose using the declared content of C_{25}H_{31}F_{3}O_{5}S, 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 for Pressurised Metered-dose Preparations for Inhalation.

Related substances

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

Solution A  30 volumes of water and 70 volumes of a solution containing 0.05% v/v of orthophosphoric acid in methanol.

(1) Dissolve, with the aid of ultrasound, a quantity of the powder in sufficient solution A to produce a solution containing 0.02% w/v of Fluticasone Propionate.

(2) Dissolve, with the aid of ultrasound, a quantity of the powder in sufficient solution A to produce a solution containing the equivalent of 0.01% w/v of salmeterol.

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

(4) 0.00036% w/v of salmeterol xinafoate impurity 1 BPCRS.

(5) 0.000015% w/v of salmeterol xinafoate impurity 1 BPCRS.

(6) 0.02% w/v of fluticasone propionate BPCRS and 0.00006% w/v of fluticasone S-methyl BPCRS (fluticasone propionate impurity D).

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* 0.05M ammonium dihydrogen orthophosphate adjusted to pH 2.9 with 10% v/v of orthophosphoric acid.

*Mobile phase B* acetonitrile.

<table>
<thead>
<tr>
<th>Time (Minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>70</td>
<td>30</td>
<td>isocratic</td>
</tr>
<tr>
<td>1-61</td>
<td>70→22</td>
<td>30→78</td>
<td>linear gradient</td>
</tr>
<tr>
<td>61-62</td>
<td>22→70</td>
<td>78→30</td>
<td>linear gradient</td>
</tr>
<tr>
<td>62-71</td>
<td>70</td>
<td>30</td>
<td>re-equilibration</td>
</tr>
</tbody>
</table>

When the chromatograms are recorded under the prescribed conditions the retention times relative to fluticasone propionate (retention time about 37 minutes) are: salmeterol, about 0.41; impurity 1, about 0.74; fluticasone propionate impurity D, about 0.97 and fluticasone propionate impurity G, about 1.1.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (6), the resolution between the peaks due to 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% of each);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

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 principal peak in the chromatogram obtained with solution (3) (0.1%).

*For salmeterol* In the chromatogram obtained with solution (2):
the area of any peak corresponding to impurity 1 is not greater than the area of the principal peak in the chromatogram obtained with solution (4) (2.5%);

the area of any other secondary peak is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other secondary peaks is not greater than ten times the area of the principal peak in the chromatogram obtained with solution (5) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

**ASSAY**

*For fluticasone propionate* Use the average of the individual results obtained in the test for Uniformity of delivered dose.

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

**LABELLING**

The quantity of Salmeterol Xinafoate is stated in terms of the equivalent amount of salmeterol.

**IMPURITIES**

The impurities limited by the requirements of this monograph include:

A, C, D, E, F, G and H listed under Fluticasone Propionate;

A, B, C, E and G listed under Salmeterol Xinafoate;