| | |
|---|---|
| **EAG/Panel/Working Party** | Medicinal Chemicals 2 |
| **Contact Details** | helen.corns@mhra.gov.uk<br>sarah.gomersal@mhra.gov.uk |
| **Deadline for Comment** | 31 March 2018 |
| **Notes**: Draft new monograph | |

# Salmeterol Pressurised Inhalation, Suspension

Salmeterol Preparations

**Action and use**
Beta$_2$-adrenoceptor agonist; bronchodilator.

**DEFINITION**

Salmeterol Pressurised Inhalation Suspension is a suspension of 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.*

**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 salmeterol, $C_{25}H_{37}NO_4$**
85 to 115% of the stated delivered dose (ex-actuator).

**IDENTIFICATION**

A. Cool the contents of the pressurised container, remove the valve assembly and allow the propellant to evaporate. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of Salmeterol Xinafoate *(RS XXX)*.

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**

**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 II 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* to produce a solution containing the equivalent of 0.000042% w/v of salmeterol.

(2) 0.000042% w/v *salmeterol xinafoate EPCRS* in *methanol.*

(3) 0.000042% w/v *salmeterol xinafoate EPCRS* and 0.000003% w/v *salmeterol xinafoate impurity F BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (5.0 cm × 3.0 mm) packed *octadecylsilyl silica gel for chromatography* (5µm) (Hypersil ODS is suitable).

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

(c) Use a flow rate of 1 mL per minute.

(d) Use a column temperature of 40°.

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

(f) Inject 100 µL of each solution.

*MOBILE PHASE*

1 volume of 0.0025M *sodium dodecyl sulfate* containing 1% v/v *glacial acetic acid* and 10 volumes of *methanol.*

When the chromatograms are recorded under the prescribed conditions the relative retentions to salmeterol (retention time of about 2.6 minutes) are: impurity F, 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 salmeterol and impurity F is at least 1.5.

DETERMINATION OF CONTENT

Calculate the content of salmeterol, $C_{25}H_{37}NO_4$, per delivered dose using the declared content of $C_{36}H_{45}NO_7$ in *salmeterol xinafoate EPCRS*. Each mg of $C_{36}H_{45}NO_7$ is equivalent to 0.6880 mg of $C_{25}H_{37}NO_4$. 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.

*Solution A* A mixture of equal volumes of *acetonitrile* and *water*.

(1) Prepare the sample in an appropriate manner and dissolve the sample in sufficient solution A to produce a solution containing the equivalent of 0.02% w/v of salmeterol.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.054% w/v *salmeterol xinafoate for system suitability EPCRS* in solution A.

(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5µm) (X Terra MS-C18 is suitable).

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

(c) Use a flow rate of 1.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 225 nm.

(f) Inject 20 µL of each solution.

*MOBILE PHASE*

*Solution A* Dilute 1 volume of 1M *potassium dihydrogen phosphate*, previously adjusted to pH 2.5 with *orthophosphoric acid*, to 100 volumes with *water*.

*Mobile phase A* 0.005M *sodium dodecyl sulfate* in a mixture of equal volumes of solution B and *acetonitrile*.

*Mobile phase B* 0.005M *sodium dodecyl sulfate* in a mixture of 2 volumes of solution B and 8 volumes of *acetonitrile*.

| Time (Minutes) | Mobile phase A% | Mobile phase B% | Comment |
|---|---|---|---|
| 0-5 | 100 | 0 | isocratic |
| 5-20 | 100→0 | 0→100 | linear gradient |
| 20-25 | 0 | 100 | isocratic |
| 25-26 | 0→100 | 100→0 | linear gradient |
| 26-31 | 100 | 0 | re-equilibration |

When the chromatograms are recorded under the prescribed conditions the retention times relative to salmeterol (retention time of about 12 minutes) are: impurity A, about 0.4; impurity B, about 0.7; impurity C, about 0.85; impurity D, about 0.93; impurity E, about 0.96; impurity F, about 1.2; impurity G, about 2.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to salmeterol and salmeterol impurity E is at least 1.5.

LIMITS

In the chromatogram obtained with solution (1):

identify any peaks corresponding to impurity D and multiply the area of this peak by a correction factor of 0.7;

the area of any peak corresponding to salmeterol impurity G is not greater than twice the area of the principal peak in the chromatogram obtained with solution (4) (0.2%);

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

the sum of the areas of all impurities is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak 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 active ingredient in terms of the equivalent delivered dose.

**IMPURITIES**

The impurities limited by the requirements of this monograph include impurities A, B, C, D, E, F and G from Salmeterol Xinafoate monograph.