Salmeterol Pressurised Inhalation, Suspension

Salmeterol Preparations

Action and use
Betα-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 II 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 225 nm 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.

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_{25}H_{37}NO_{4} in salmeterol xinafoate EPCRS. Each mg of C_{25}H_{37}NO_{4} 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 octadecylsilica gel for chromatography (5 µm) (XTerra 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°C.
(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.