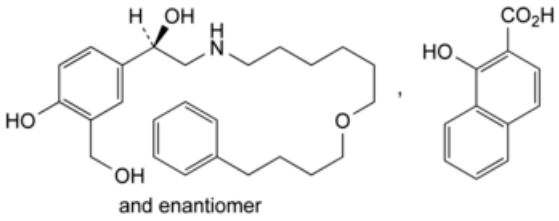
Edition: BP 2025 (Ph. Eur. 11.6 update)

Salmeterol Xinafoate

General Notices

(Ph. Eur. monograph 1765)



$C_{36}H_{45}NO_7$ 604 *94749-08-3*

Action and use

Beta$_2$-adrenoceptor agonist; bronchodilator.

Preparations

Fluticasone and Salmeterol Inhalation Powder, pre-metered

Fluticasone and Salmeterol Inhalation Powder

Fluticasone and Salmeterol Pressurised Inhalation, Suspension

Salmeterol Inhalation Powder, pre-metered

Salmeterol Pressurised Inhalation, Suspension

Ph Eur

DEFINITION

(1*RS*)-1-[4-Hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol 1-hydroxynaphthalene-2-carboxylate.

Content

97.5 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Practically insoluble in water, soluble in methanol, slightly soluble in anhydrous ethanol, practically insoluble in methylene chloride.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *salmeterol xinafoate CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29). *Protect the solutions from light*.

Solvent mixture *acetonitrile R*, *water R* (50:50 *V/V*).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dissolve 25.0 mg of the substance to be examined in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (a) Dissolve the contents of a vial of *salmeterol xinafoate for system suitability CRS* (containing impurities E and G) in 1 mL of the solvent mixture.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of *salmeterol xinafoate for peak identification CRS* (containing impurity D) in the solvent mixture and dilute to 1.0 mL with the solvent mixture.

Reference solution (d) Dissolve 25.0 mg of *salmeterol xinafoate CRS* in mobile phase A and dilute to 100.0 mL with mobile phase A.

Reference solution (e) Dilute 1.0 mL of reference solution (a) to 20.0 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 24 volumes of a 7.71 g/L solution of *ammonium acetate R* and 24 volumes of a 28.84 g/L solution of *sodium dodecyl sulfate R* and adjust to pH 2.7 with *glacial acetic acid R*; mix with 52 volumes of *acetonitrile R*;

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 16	100	0
16 - 36	100 → 30	0 → 70
36 - 45	30	70

Flow rate 2 mL/min.

Detection Spectrophotometer at 278 nm.

Injection 20 µL of test solution (a) and reference solutions (a), (b) and (c).

Identification of impurities Use the chromatogram supplied with *salmeterol xinafoate for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities E and G; use the chromatogram supplied with *salmeterol xinafoate for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention With reference to salmeterol (retention time = about 13 min): xinafoic acid = about 0.2; impurity D = about 0.8; impurity E = about 0.9; impurity G = about 2.7.

System suitability Reference solution (a):

— *peak-to-valley ratio*: minimum 10, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to salmeterol.

Calculation of percentage contents:

— for each impurity, use the concentration of salmeterol xinafoate in reference solution (b).

Limits:

— *impurities D, G*: for each impurity, maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent; disregard the peak due to xinafoic acid.

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Mobile phase Mobile phase A.

Injection 20 µL of test solution (b) and reference solutions (d) and (e).

Run time Until complete elution of the peak due to salmeterol (about 16 min).

System suitability Reference solution (e):

— *peak-to-valley ratio*: minimum 10, where H_p = height above the baseline of the peak due to impurity E and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to salmeterol.

Calculate the percentage content of $C_{36}H_{45}NO_7$ using the chromatogram obtained with reference solution (d) and taking into account the assigned content of *salmeterol xinafoate CRS*.

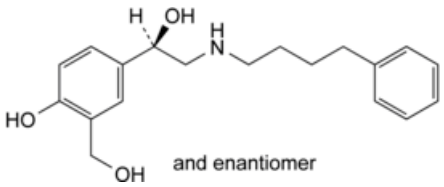
STORAGE

Protected from light.

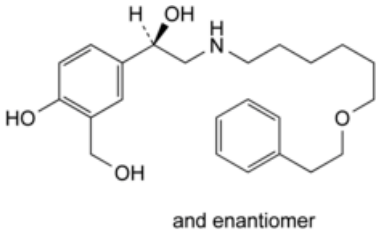
IMPURITIES

Specified impurities D, G.

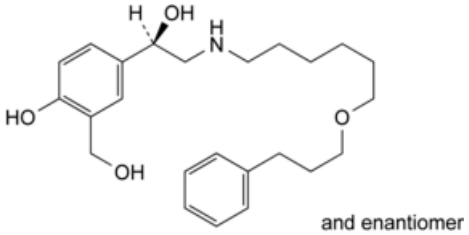
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B, C, E, F.



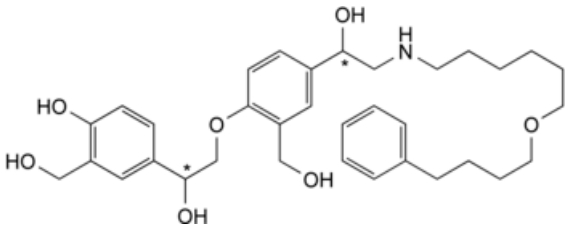
A. (1*RS*)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[(4-phenylbutyl)amino]ethanol,



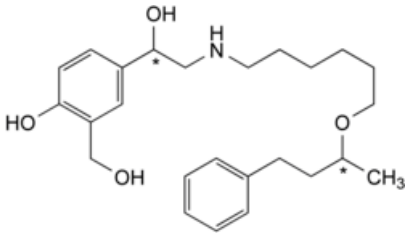
B. (1*RS*)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(2-phenylethoxy)hexyl]amino]ethanol,



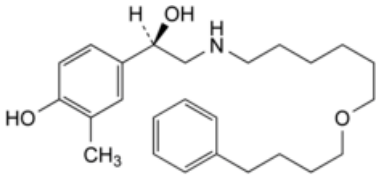
C. (1*RS*)-1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(3-phenylpropoxy)hexyl]amino]ethanol,



D. 1-[4-[2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethoxy]-3-(hydroxymethyl)phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol,

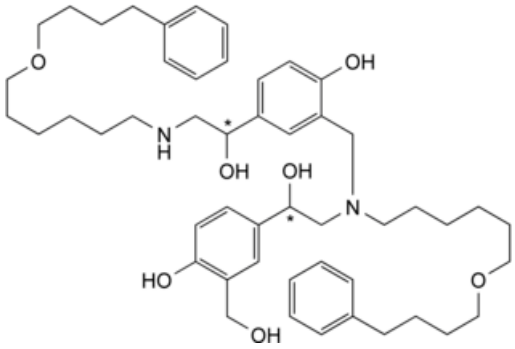


E. 1-[4-hydroxy-3-(hydroxymethyl)phenyl]-2-[[6-(1-methyl-3-phenylpropoxy)hexyl]amino]ethanol,



and enantiomer

F. (1*RS*)-1-(4-hydroxy-3-methylphenyl)-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol,



G. 1-[4-hydroxy-3-[[[2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl][6-(4-phenylbutoxy)hexyl]amino]methyl]phenyl]-2-[[6-(4-phenylbutoxy)hexyl]amino]ethanol.

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