Salmeterol Xinafoate

Type of Posting	Revision Bulletin
Posting Date	28–Jul–2017
Official Date	01–Aug–2017
Expert Committee	Chemical Medicine Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Salmeterol Xinafoate monograph. The purpose for the revision is to revise the resolution requirement from NLT 1.2 to the original requirement of NLT 1.0 because comments were received noting that the requirement of NLT 1.2 was not achievable and the original requirement of NLT 1.0 was suitable. Additionally, the second name for Salmeterol Xinafoate Related Compound B has been deleted, as it is incorrect.

The Salmeterol Xinafoate_ Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement* to *USP 41–NF 36*.

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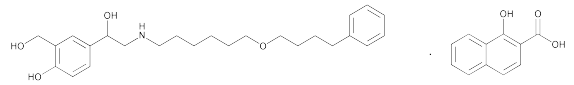
Should you have any questions, please contact Ravi Ravichandran, Principal Scientific Liaison, (301–816–8330 or rr@usp.org).

Salmeterol Xinafoate



$C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ 603.75

1,3-Benzenedimethanol, 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-, (±)-, 1-hydroxy-2-naphthalenecarboxylate (salt);
(±)-4-Hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-*m*-xylene-α,α'-diol 1-hydroxy-2-naphthoate (salt) [94749-08-3].

DEFINITION

Salmeterol Xinafoate contains NLT 98.0% and NMT 102.0% of salmeterol xinafoate ($C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$), calculated on the water- and solvent-free basis.

IDENTIFICATION

Change to read:

• **A. ■INFRARED ABSORPTION ⟨197⟩:** [NOTE—⟨197A⟩, ⟨197K⟩, or ⟨197M⟩ may be used.]■2S *(USP40)*
• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

• **PROCEDURE**
■[NOTE—It is recommended that solutions containing salmeterol be protected from light.]■1S *(USP40)*
Buffer A: 0.1 M sodium dodecyl sulfate
Buffer B: 0.1 M ammonium acetate
Mobile phase: Acetonitrile, *Buffer A*, and *Buffer B* (52:24:24). Adjust with glacial acetic acid to a pH of 3.8. ■[NOTE—This may need as much as 75 mL of glacial acetic acid for each liter.]■1S *(USP40)*
System suitability solution: ■0.25 mg/mL of USP Salmeterol Xinafoate RS and 0.02 mg/mL of USP Salmeterol Related Compound B RS in *Mobile phase*■1S *(USP40)*
Standard solution: 0.25 mg/mL of USP Salmeterol Xinafoate RS in *Mobile phase*
Sample solution: 0.25 mg/mL of Salmeterol Xinafoate in *Mobile phase*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 278 nm
Column: 4.6-mm × 15-cm; ■5-µm■1S *(USP40)* packing L1
Flow rate: 2 mL/min
Injection volume: 20 µL
System suitability
Sample: *System suitability solution*
■[NOTE—The relative retention times for salmeterol related compound B and salmeterol are about 0.9 and 1.0, respectively.]■1S *(USP40)*
Suitability requirements
Resolution: ■NLT •1.0● (RB 1-Aug-2017) between salmeterol and salmeterol related compound B■1S *(USP40)*
Relative standard deviation: ■NMT 1.0%■1S *(USP40)* for salmeterol
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of salmeterol xinafoate ($C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$) in the portion of Salmeterol Xinafoate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Salmeterol Xinafoate RS in the *Standard solution* (mg/mL)
C_U = concentration of Salmeterol Xinafoate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the water- and solvent-free basis

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

Change to read:

• **ORGANIC IMPURITIES**
[NOTE—■It is recommended that solutions containing salmeterol be protected from light.■1S *(USP40)*]
Buffer A, Buffer B, and **Chromatographic system:** Proceed as directed in the *Assay*.
Diluent: Acetonitrile and water (50:50)
■**Solution A:**■1S *(USP40)* Acetonitrile, *Buffer A*, and *Buffer B* (52:24:24). Adjust with glacial acetic acid to a pH of 3.8.
■**Solution B:**■1S *(USP40)* Acetonitrile
Mobile phase: See *Table 1*.

Table 1

Time (min)	■Solution A■1S *(USP40)* (%)	■Solution B■1S *(USP40)* (%)
0	100	0
16.0	100	0
36.0	30	70
45.0	30	70
45.1■1S *(USP40)*	100	0
■50[a]	100[a]	0[a]■1S *(USP40)*

[a] The required equilibration time may be modified to achieve a stable baseline.■1S *(USP40)*

■**System suitability solution:** 5.0 mg/mL of USP Salmeterol Xinafoate RS and 0.3 mg/mL each of USP Salmeterol Related Compound A RS and USP Salmeterol Related Compound B RS in *Diluent*■1S *(USP40)*
Sample solution: 5.0 mg/mL of Salmeterol Xinafoate in *Diluent*
System suitability
Sample: ■*System suitability solution*
[NOTE—See *Table 2* for relative retention times.]■1S *(USP40)*
Suitability requirements
Resolution: ■NLT •1.0● (RB 1-Aug-2017) between salmeterol and salmeterol related compound B■1S *(USP40)*
Tailing factor: NMT 2.5 for salmeterol ■■1S *(USP40)*
Analysis
[NOTE—Disregard the peak due to hydroxynaphthoic acid and any peaks from blank injections.]
Sample: *Sample solution*
Calculate the percentage of any individual impurity in the portion of Salmeterol Xinafoate taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 2*. [NOTE—Calculate the total impurities from the sum of all impurity peaks greater than or equal to 0.05%.]

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Hydroxynaphthoic acid[a]	0.2	—
Salmeterol related compound A	0.3	0.2
Salmeterol-phenylethoxy[b]	0.5	0.1
Salmeterol-phenylpropoxy[c]	0.7	0.1
Salmeterol-*O*-alkyl[d]	0.8	0.3
Salmeterol related compound B	0.9	0.1
Salmeterol ■■1S *(USP40)*	1.0	—
Salmeterol-deoxy[e]	1.6	0.2
Salmeterol-*N*-alkyl[f]	2.7	0.2
Any unspecified impurity	—	0.10
■■1S *(USP40)*	■■1S *(USP40)*	■■1S *(USP40)*
Total impurities	—	0.9

[a] 1-Hydroxy-naphthalene-2-carboxylic acid. This is the counter ion of salmeterol and is included for identification only.
[b] 4-[1-Hydroxy-2-(6-phenethoxyhexylamino)ethyl]-2-(hydroxymethyl)phenol.
[c] 4-{1-Hydroxy-2-[6-(3-phenylpropoxy)hexylamino]ethyl}-2-(hydroxymethyl)phenol.
[d] 4-{1-Hydroxy-2-[4-{1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}-2-(hydroxymethyl)phenoxy]ethyl}-2-(hydroxymethyl)phenol.
[e] 4-{1-Hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}-2-methylphenol.
[f] 4-{1-Hydroxy-2-[(2-hydroxy-5-{1-hydroxy-2-[6-(4-phenylbutoxy)hexylamino]ethyl}benzyl)[6-(4-phenylbutoxy)hexyl]amino]ethyl}-2-(hydroxymethyl)phenol.

SPECIFIC TESTS

- **WATER DETERMINATION** ⟨**921**⟩**,** *Method I*
  Sample: 0.5 g
  Acceptance criteria: NMT 0.25%

Delete the following:

■• **OPTICAL ROTATION** ⟨**781S**⟩**,** *Procedures, Specific Rotation*
Sample solution: 10 mg/mL in methanol
Acceptance criteria: –0.5° to +0.5° (t = 20°), calculated on the anhydrous and solvent-free basis■1S *(USP40)*

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at a temperature not exceeding 30°.

Delete the following:

■• **LABELING:** Salmeterol Xinafoate in the form of microcrystals is so labeled.■1S *(USP40)*

Change to read:

- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Salmeterol Xinafoate RS
  USP Salmeterol Related Compound A RS
  4-[1-Hydroxy-2-(4-phenylbutylamino)ethyl]-2-(hydroxymethyl)phenol.
  $C_{19}H_{25}NO_3$ 315.41
  USP Salmeterol Related Compound B RS
  4-{1-Hydroxy-2-[6-(4-phenylbutan-2-yloxy)hexylamino]ethyl}-2-(hydroxymethyl)phenol.
  • (RB 1-Aug-2017)
  $C_{25}H_{37}NO_4$ 415.57