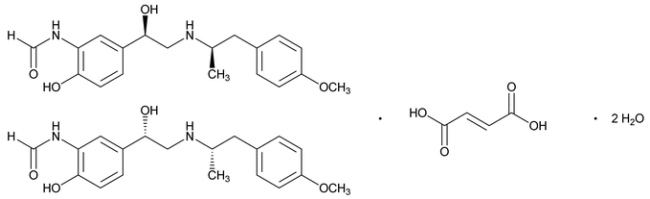
Formoterol Fumarate

Change to read:



$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ ▲840.92

Formamide, *N*-[2-hydroxy-5-[1-hydroxy-2-[[1-(4-methoxyphenyl)propan-2-yl]amino)ethyl]phenyl], (*R**,*R**)-, fumarate (2:1) (salt), dihydrate;▲ (IRA 1-Jan-2020)

(±)-2′-Hydroxy-5′-[(*R**)-1-hydroxy-2-[[(*R**)-*p*-methoxy-α-methylphenethyl]amino]ethyl]formanilide fumarate (2:1) (salt), dihydrate [183814-30-4].

▲Anhydrous

$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$ 804.89

[43229-80-7].▲ (IRA 1-Jan-2020)

DEFINITION

Formoterol Fumarate contains NLT 98.5% and NMT 101.5% of formoterol fumarate [$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$], calculated on the anhydrous basis.

IDENTIFICATION

Change to read:

- **A.** ▲**SPECTROSCOPIC IDENTIFICATION TESTS** ⟨197⟩*, Infrared Spectroscopy*:▲ (IRA 1-Jan-2020) ⟨197K⟩ ▲or ⟨197A⟩▲ (IRA 1-Jan-2020)
- **B.** The retention time of the formoterol peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**

▲Protect solutions of formoterol fumarate from light.▲ (IRA 1-Jan-2020)

Buffer: 6.1 g/L of monobasic sodium phosphate and 1.0 g/L of dibasic sodium phosphate dihydrate in water. [NOTE—The pH is 6.0 ± 0.1.]

Solution A: 3.7 g/L of monobasic sodium phosphate and 0.35 g/L of phosphoric acid in water. [NOTE—The pH is 3.1 ± 0.1.]

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	84	16
10	84	16
12.7	30	70
12.8	84	16
18	84	16

Diluent: Acetonitrile and *Buffer* (16:84)

Standard solution: 0.2 mg/mL of USP Formoterol Fumarate RS in *Diluent*

Sample solution: 0.2 mg/mL of Formoterol Fumarate in *Diluent*

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 214 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: ▲1▲ (IRA 1-Jan-2020) mL/min
Injection volume: 10 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 0.73▲%▲ (IRA 1-Jan-2020)

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of formoterol fumarate [$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$] in the portion of Formoterol Fumarate taken:

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

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

Acceptance criteria: 98.5%–101.5% on the anhydrous basis

IMPURITIES

- **RESIDUE ON IGNITION** ⟨281⟩

Sample: 1 g
Acceptance criteria: NMT 0.1%

Change to read:

- **ORGANIC IMPURITIES**

▲Protect solutions of formoterol fumarate from light.▲ (IRA 1-Jan-2020)

Buffer, Solution A, Solution B, and **Diluent:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	84	16
10	84	16
37	30	70
40	84	16
55	84	16

System suitability solution: ▲0.2 mg/mL of USP Formoterol Fumarate RS and 2 µg/mL each of USP Formoterol Related Compound A RS, USP Formoterol Related Compound C RS, and USP Formoterol Related Compound D RS▲ (IRA 1-Jan-2020) in *Diluent*. Sonicate to dissolve prior to final dilution.

▲**Sensitivity solution:** 0.1 µg/mL of USP Formoterol Fumarate RS in *Diluent*▲ (IRA 1-Jan-2020)

Sample solution: ▲0.2▲ (IRA 1-Jan-2020) mg/mL of Formoterol Fumarate in *Diluent*. Sonicate to dissolve before final dilution.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 214 nm
Column: 4.6-mm × 15-cm; packing L7
Flow rate: 1 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution* ▲and *Sensitivity solution*▲ (IRA 1-Jan-2020)
[NOTE—The relative retention times for the peaks are given in *Table 3*.]
Suitability requirements
Resolution: ▲NLT 2.0 between formoterol and formoterol related compound C; and NLT 1.5 between formoterol related compound C and formoterol related compound D,▲ (IRA 1-Jan-2020) *System suitability solution*
▲**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*▲ (IRA 1-Jan-2020)

Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Formoterol Fumarate taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_T = sum of the responses of all peaks from the *Sample solution*
F = relative response factor for each peak (see *Table 3*)

Acceptance criteria: See *Table 3*. ▲The reporting threshold is▲ (IRA 1-Jan-2020) 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
▲2-Aminopropyl anisol[a]▲ (IRA 1-Jan-2020)	0.4	1.0	0.1
Formoterol related compound A	0.5	0.57	0.3
▲Desmethyl formoterol[b]▲ (IRA 1-Jan-2020)	0.7	1.0	0.2
Formoterol	1.0	—	—
Formoterol related compound C	1.2	1.0	0.2
Formoterol related compound D	1.3	1.0	0.2
▲3-Methyl formoterol[c]▲ (IRA 1-Jan-2020)	1.8	1.0	0.1
▲Formoterol dimer[d, e]▲ (IRA 1-Jan-2020)	2.0	1.0	0.2
▲*N*-Benzyl formoterol[f]▲ (IRA 1-Jan-2020)	2.2	1.0	0.1
Any individual unspecified impurity	—	1.0	0.10

Table 3 *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Total impurities	—	—	0.5

[a] 1-(4-Methoxyphenyl)propan-2-amine.
[b] *N*-(2-Hydroxy-5-{1-hydroxy-2-[(4-methoxyphenethyl)amino]ethyl}phenyl)formamide.
[c] *N*-[2-Hydroxy-5-(1-hydroxy-2-{[1-(4-methoxy-3-methylphenyl)propan-2-yl]amino}ethyl)phenyl]formamide.
[d] *N*-[2-Hydroxy-5-(1-{[2-hydroxy-5-(1-hydroxy-2-{[1-(4-methoxyphenyl)propan-2-yl]amino}ethyl)phenyl]amino}-2-{[1-(4-methoxyphenyl)propan-2-yl]amino}ethyl)phenyl]formamide.
[e] When present in the chromatogram, the formoterol dimer diastereomers will appear as multiple overlapped peaks, for which the total peak area is to be assessed.
[f] *N*-{5-[(*RS*)-2-{Benzyl[(*RS*)-1-(4-methoxyphenyl)propan-2-yl]amino}-1-hydroxyethyl]-2-hydroxyphenyl}formamide.

Change to read:

• **LIMIT OF FORMOTEROL RELATED COMPOUND I**
Buffer: 4.2 g/L of tribasic potassium phosphate. Adjust with potassium hydroxide or phosphoric acid to a pH of 12.0 ± 0.1.
Mobile phase: Acetonitrile and *Buffer* (12:88)
System suitability solution: 0.1 mg/mL of USP Formoterol Fumarate Resolution Mixture RS ▲in water▲ (IRA 1-Jan-2020)
Sample solution: 0.1 mg/mL of Formoterol Fumarate ▲in water▲ (IRA 1-Jan-2020)
Diluted sample solution: 0.2 µg/mL of Formoterol Fumarate from the *Sample solution* ▲in water▲ (IRA 1-Jan-2020)
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 15-cm; packing L67
Flow rate: 0.5 mL/min
Injection volume: 20 µL
▲**Run time:** NLT 2 times the retention time of formoterol▲ (IRA 1-Jan-2020)
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for formoterol and formoterol related compound I are 1.0 and 1.17, respectively.]
Suitability requirements
Peak-to-valley ratio: NLT 2.5 for formoterol related compound I and formoterol
Analysis
Samples: *Sample solution* and *Diluted sample solution*
Acceptance criteria: NMT 0.3%; the peak area of formoterol diastereomer in the *Sample solution* is NMT 1.5 times the peak area of formoterol fumarate in the *Diluted sample solution*.

SPECIFIC TESTS

• **pH** ⟨791⟩
Sample solution: 1 mg/mL in water
Acceptance criteria: 5.5–6.5
• **WATER DETERMINATION** ⟨921⟩**,** *Method I***:** 4.0%–5.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed light-resistant containers.

Change to read:

• **USP REFERENCE STANDARDS** ⟨11⟩
USP Formoterol Fumarate RS
USP Formoterol Fumarate Resolution Mixture RS

Mixture of formoterol and formoterol related compound I.

Formoterol related compound I: ▲*N*-(2-Hydroxy-5-[(*RS*)-1-hydroxy-2-{[(*SR*)-1-(4-methoxyphenyl)propan-2-yl]amino}ethyl]phenyl)formamide.

USP Formoterol Related Compound A RS
2-Amino-4-(1-hydroxy-2-((1-(4-methoxyphenyl)propan-2-yl)amino)ethyl)phenol.
$C_{18}H_{24}N_2O_3$ 316.39

USP Formoterol Related Compound C RS
N-(2-Hydroxy-5-(1-hydroxy-2-{[1-(4-methoxyphenyl)propan-2-yl]amino}ethyl)phenyl)acetamide fumarate.
$(C_{20}H_{26}N_2O_4)_2 \cdot C_4H_4O_4$ 832.95

USP Formoterol Related Compound D RS
N-(2-Hydroxy-5-(1-hydroxy-2-{[1-(4-methoxyphenyl)propan-2-yl](methyl)amino}ethyl)phenyl)formamide fumarate.
$(C_{20}H_{26}N_2O_4)_2 \cdot C_4H_4O_4$ 832.95▲ (IRA 1-Jan-2020)