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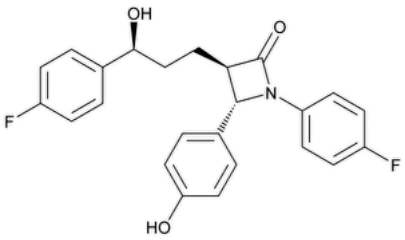
Ezetimibe



$C_{24}H_{21}F_2NO_3$ 409.43

2-Azetidinone, 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-, [3*R*-[3α(*S**),4β]]-; (3*R*,4*S*)-1-(*p*-Fluorophenyl)-3-[(3*S*)-3-(*p*-fluorophenyl)-3-hydroxypropyl]-4-(*p*-hydroxyphenyl)-2-azetidinone; (3*R*,4*S*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-azetidin-2-one CAS RN®: 163222-33-1; UNII: EOR26LQQ24.

DEFINITION

Ezetimibe contains NLT 98.0% and NMT 102.0% of ezetimibe ($C_{24}H_{21}F_2NO_3$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197M

• **B.** The ratio of the retention time of the ezetimibe peak of the *Sample solution* to that of the *System suitability solution* obtained in *Organic Impurities, Procedure 2* is between 0.97 and 1.03.

ASSAY

Change to read:

• **Procedure**

Solution A: Water

Solution B: Acetonitrile

Solution C: Methanol

Mobile phase: See *Table 1*. ▲Adjust the percentages of *Solution A* and *Solution B* to achieve a retention time of about 33 min for the ezetimibe peak. The percentage of *Solution C* should remain unchanged.

[Note—Ezetimibe and related impurities are sensitive to small variations in *Mobile phase* composition, which may affect resolution and retention characteristics.]▲ (USP 1-Aug-2024)

Table 1

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	▲66▲ (USP 1-Aug-2024)	▲24▲ (USP 1-Aug-2024)	10
37	▲66▲ (USP 1-Aug-2024)	▲24▲ (USP 1-Aug-2024)	10
60	40	50	10
70	40	50	10
80	10	80	10
90	10	80	10
90.1	▲66▲ (USP 1-Aug-2024)	▲24▲ (USP 1-Aug-2024)	10

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
100	▲66▲ (USP 1-Aug-2024)	▲24▲ (USP 1-Aug-2024)	10

Diluent: Acetonitrile, methanol, and water ▲(27:10:63).▲ (USP 1-Aug-2024) Add 1.0 mL of glacial acetic acid per each liter of the mixture.

Standard solution: 0.25 mg/mL of USP Ezetimibe RS prepared as follows. Transfer a suitable amount of USP Ezetimibe RS to a suitable volumetric flask. Dissolve in about 1%–2% of the flask volume of acetonitrile, and dilute with *Diluent* to volume. [NOTE—The *Standard solution* contains a detectable level of *o*-fluorobenzene isomer (approximately 0.04%) from USP Ezetimibe RS.]

Sample solution: 0.25 mg/mL of Ezetimibe prepared as follows. Transfer a suitable amount of Ezetimibe to a suitable volumetric flask. Dissolve in about 1%–2% of the flask volume of acetonitrile, and dilute with *Diluent* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detectors

0–5 min: UV 215 nm

5–100 min: UV 248 nm

Column: 4.6-mm × 15-cm; 5-µm packing L43

Flow rate: 2 mL/min

Injection volume: 60 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5 for ezetimibe

Relative standard deviation: NMT 0.73% for ezetimibe

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ezetimibe ($C_{24}H_{21}F_2NO_3$) in the portion of Ezetimibe taken:

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

r_U = peak response of ezetimibe from the *Sample solution*

r_S = peak response of ezetimibe from the *Standard solution*

C_S = concentration of USP Ezetimibe RS in the *Standard solution* (mg/mL)

C_U = concentration of Ezetimibe in the *Sample solution* (mg/mL)

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

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.2%

Change to read:

• **ORGANIC IMPURITIES, PROCEDURE 1**

▲**Solution A, Solution B, Solution C,**▲ (USP 1-Aug-2024) **Mobile phase, Diluent, Standard solution, Sample solution,** and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.125 µg/mL of USP Ezetimibe RS from the *Standard solution* in *Diluent*

System suitability

Samples: *Standard solution* and *Sensitivity solution*

▲[NOTE—The relative retention times in *Table 2* are provided as information that could aid in peak assignment.]

Table 2▲ (USP 1-Aug-2024)

Name	Relative Retention Time
Desfluoroaniline analog[a]	0.72
Ezetimibe diastereomers[b]	0.77

Name	Relative Retention Time
o-Fluorobenzene isomer	0.89
Ezetimibe	1.0
m-Fluoroaniline analog[c]	1.13
Ezetimibe ketone[d]	1.42

[a] (3*R*,4*S*)-3-[(*S*)-3-(4-Fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-1-phenylazetidin-2-one.

[b] The two ezetimibe diastereomers, *R*,*R*,*R*- and *S*,*S*,*S*-, elute as one peak ▲▲ (USP 1-Aug-2024) .

[c] (3*R*,4*S*)-1-(3-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

[d] (3*R*,4*S*)-1-(4-Fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

Suitability requirements

Resolution: NLT 1.5 between ezetimibe and *o*-fluorobenzene isomer, *Standard solution*

Tailing factor: NMT 1.5 for ezetimibe, *Standard solution*

Relative standard deviation: NMT 10% for ezetimibe, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of ▲any impurity▲ (USP 1-Aug-2024) in the portion of Ezetimibe 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 all peak responses from the *Sample solution*

F = relative response factor from *Table 3*

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
Desfluoroaniline analog	1.0	0.2
▲		▲ (USP 1-Aug-2024)
o-Fluorobenzene isomer	1.0	0.2
▲		▲ (USP 1-Aug-2024)
m-Fluoroaniline analog	1.0	0.2
Ezetimibe ketone	1.5	0.1
Any unspecified impurity▲[a]▲ (USP 1-Aug-2024)	1.0	0.10
Total impurities▲[a]▲ (USP 1-Aug-2024)	—	0.6

▲a Excludes ezetimibe diastereomers, which are quantitated using *Organic Impurities, Procedure 2*.▲ (USP 1-Aug-2024)

Change to read:

• **Organic Impurities, Procedure 2**

Mobile phase: Acetonitrile and water (45:55)

Diluent: Acetonitrile with 0.1% glacial acetic acid (v/v)

System suitability solution: 0.4 mg/mL of USP Ezetimibe System Suitability Mixture RS in *Diluent*

Sensitivity solution: 0.2 µg/mL of USP Ezetimibe RS in *Diluent*

Sample solution: 0.4 mg/mL of Ezetimibe in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 248 nm

Column: Two columns in series of 4.6-mm × 15-cm; 5-µm packing L93

Column temperature: 5°

Flow rate: 0.35 mL/min

Injection volume: 10 µL

Run time: NLT 1.4 times the retention time of the ezetimibe peak

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

▲[NOTE—The relative retention times in *Table 4* are provided as information that could aid in peak assignment.]

Table 4▲ (USP 1-Aug-2024)

Name	Relative Retention Time
S,S,S-Ezetimibe[a]	0.76
R,R,R-Ezetimibe[b]	0.82
Desfluoroaniline analog[c]	0.89
R,R,S-Ezetimibe	0.93
Ezetimibe	1.00
S,S,R-Ezetimibe[d]	1.12
R,S,R-Ezetimibe[e]	1.22

[a] (3*S*,4*S*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

[b] (3*R*,4*R*)-1-(4-Fluorophenyl)-3-[(*R*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

[c] Desfluoroaniline analog impurity is quantitated using *Procedure 1*.

[d] (3*S*,4*R*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

[e] (3*S*,4*R*)-1-(4-Fluorophenyl)-3-[(*R*)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

Suitability requirements

Resolution: NLT 1.5 between ezetimibe and *R,R,S*-ezetimibe diastereomer, *System suitability solution*

Tailing factor: NMT 1.5 for ezetimibe, *System suitability solution*

Relative standard deviation: NMT 10% for ezetimibe, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each enantiomeric or diastereomeric impurity in the portion of Ezetimibe 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 peak responses from the *Sample solution*

Acceptance criteria: See *Table 5*. The reporting threshold is 0.05%.

Table 5

	Acceptance

[a] Sum of all impurities from *Organic Impurities, Procedure 1* and *Procedure 2*.

SPECIFIC TESTS

- **Water Determination** ⟨921⟩, *Method I, Method Ia* or *Method Ic*: NMT 0.6%
- **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

Sample solution: 10 mg/mL of Ezetimibe previously dried for NLT 16 h over anhydrous calcium sulfate in methanol
Temperature: 20°
Acceptance criteria: −25.0° to −30.0°

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Protect from moisture and store below 25°.

Change to read:

- **USP Reference Standards** ⟨11⟩

USP Ezetimibe RS

It also contains a very small amount of *o*-fluorobenzene isomer.

(3*R*,4*S*)-1-(4-Fluorophenyl)-3-[(*S*)-3-(2-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one.

$C_{24}H_{21}F_2NO_3$ 409.43

USP Ezetimibe System Suitability Mixture RS

It contains a mixture of the following 3 compounds:

Ezetimibe.

o-Fluorobenzene isomer.

R,R,S-Ezetimibe.

Name	Criteria, NMT (%)
S,S,S-Ezetimibe	0.2
R,R,R-Ezetimibe	0.1
R,R,S-Ezetimibe	0.4
S,S,R-Ezetimibe	0.1
R,S,R-Ezetimibe	0.1
Total impurities[a]	0.5
Total impurities	0.9

▲ (USP 1-Aug-2024)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
EZETIMIBE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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