Ezetimibe Tablets

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Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Ezetimibe Tablets. The purpose for the revision is to add *Dissolution Test 2* to accommodate the FDA approved drug products with different dissolution conditions and tolerance than the existing dissolution test.

The Ezetimibe Tablets Revision Bulletin supersedes the currently official Ezetimibe Tablets. The Revision Bulletin will be incorporated in the *Second Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Edith Chang, Scientific Liaison (301–816–8392 or YEC@usp.org.)

Ezetimibe Tablets

DEFINITION

Ezetimibe Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution,* as obtained in the *Assay*.
- **B.** The UV absorption spectrum of the ezetimibe peak of the *Sample solution* exhibits maxima and minima at the same wavelengths as those of the corresponding peak of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water.

Mobile phase: Tetrahydrofuran, acetonitrile, and *Buffer* (100:250:650)

Diluent: Acetonitrile, glacial acetic acid, and water (600:1:400)

Standard solution: 0.2 mg/mL of USP Ezetimibe RS in *Diluent*. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate.

Sample solution: Nominally 0.2 mg/mL of ezetimibe in *Diluent* prepared as follows. Place NLT 10 powdered Tablets in a suitable volumetric flask, add *Diluent* to fill about 60% of the total volume, sonicate for about 30 min, and shake on a wrist shaker for about 45 min. Dilute with *Diluent* to volume, pass through a suitable filter of 0.45-µm pore size, and discard the first 3 mL of the filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 232 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 30 µL
Run time: NLT 2.4 times the retention time of the ezetimibe peak

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 1.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) in the portion of Tablets 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 = nominal concentration of ezetimibe in the *Sample solution* (mg/mL)

Acceptance criteria: 93.0%–107.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩

●**Test 1**● (RB 1-Feb-2018)
Do not refrigerate solutions containing ezetimibe.
Medium: 0.45% sodium lauryl sulfate in 0.05 M sodium acetate buffer, pH 4.5, prepared as follows. To 6 L of water in a suitable flask, add about 27 g of sodium lauryl sulfate and 24.6 g of sodium acetate. Dissolve the reagents by stirring until the solution is clear. Adjust with either hydrochloric acid or sodium hydroxide to a pH of 4.5; 500 mL.
Apparatus 2: 50 rpm
Time: 30 min
Standard solution: 0.02 mg/mL of USP Ezetimibe RS in *Medium* prepared as follows. To a suitable amount of USP Ezetimibe RS in an appropriate volumetric flask, add methanol to fill about 1% of the total volume, and shake until completely dissolved. Dilute with *Medium* to volume.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first 3 mL of the filtrate.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelength: 233 nm
Cell: 1.0 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Ezetimibe RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 500 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) is dissolved.

●**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Apparatus 2, Standard solution, Sample solution, Instrumental conditions, and **Analysis:** Proceed as directed in *Test 1*.
Buffer: 6.8 g/L of sodium acetate pH 4.5 prepared as follows. Dissolve 6.8 g of sodium acetate in 1 L of water. Add 3 mL of glacial acetic acid and mix. If necessary, adjust with 2 N acetic acid or 0.2 N sodium hydroxide to a pH of 4.5.
Medium: 0.45% (w/v) sodium dodecyl sulfate in *Buffer*; 500 mL
Time: 20 min
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0% for 5 replicate readings
Tolerances: NLT 80% (*Q*) of the labeled amount of ezetimibe ($C_{24}H_{21}F_2NO_3$) is dissolved.● (RB 1-Feb-2018)

- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**

Buffer, Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: Weigh about 20 mg of USP Ezetimibe RS into a 100-mL volumetric flask. Dissolve in 10 mL of 0.01 N alcoholic sodium hydroxide. Place the capped volumetric flask into a 55° oven for 15 min. Remove from the oven and immediately add 2 mL of 0.1 N hydrochloric acid and about 50 mL of *Diluent*. Mix, allow to cool to room temperature, and dilute with *Diluent* to volume. Pass through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate. [NOTE—Unidentified peak 2 with a relative retention time of about 1.14 is generated during hydrolysis.]

Sensitivity solution: 0.1 µg/mL of USP Ezetimibe RS in *Diluent*

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between the ezetimibe peak and unidentified peak 2, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each degradation product in the portion of Tablets 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 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Unidentified peak 1	0.64	—
S,S,S-Ezetimibe and *R,R,R*-Ezetimibe[a,b]	0.78	—
Ezetimibe	1.00	—
Unidentified peak 2	1.14	—
Ezetimibe tetrahydropyran analog[c]	1.53	0.2
Ezetimibe ketone[d]	1.75	0.2
Any unspecified impurity	—	0.2
Total impurities[e]	—	0.5

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

[b] Process-related impurity and controlled in the drug substance.

[c] *N*,6-Bis(4-fluorophenyl)-2-(4-hydroxyphenyl)tetrahydro-2*H*-pyran-3-carboxamide.

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

[e] Total impurities include specified and unspecified degradation products. Process impurities are not included.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Protect from moisture. Store at controlled room temperature.

Add the following:

•• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.• (RB 1-Feb-2018)

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Ezetimibe RS