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Clarithromycin Extended-Release Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-clarithromycin-ert-20231117.

DEFINITION

Clarithromycin Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$).

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*.

ASSAY

• **Procedure**

Buffer A: 0.067 M monobasic potassium phosphate

Mobile phase: Methanol and *Buffer A* (13:7). Adjust with phosphoric acid to a pH of 4.0. Pass through a suitable filter.

Standard stock solution: 625 µg/mL of clarithromycin from USP Clarithromycin RS in methanol. Shake and sonicate, if necessary, to facilitate dissolution.

Standard solution: 125 µg/mL of clarithromycin in *Mobile phase* from *Standard stock solution*. Pass through a suitable filter.

System suitability stock solution: 625 µg/mL of USP Clarithromycin Related Compound A RS in methanol

System suitability solution: 125 µg/mL of USP Clarithromycin Related Compound A RS from *System suitability stock solution* and 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*

Sample stock solution: Transfer nominally 2000 mg of clarithromycin from finely powdered Tablets to a 500-mL volumetric flask with the aid of methanol. Add about 350 mL of methanol, and shake by mechanical means for 30 min. Dilute with methanol to volume, and sonicate for 30 min. Cool to room temperature, and allow to stand for at least 16 h. Mix, allow any insoluble matter to settle, and use the supernatant.

Sample solution: Transfer 3.0 mL of the *Sample stock solution* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Columns

Guard (optional)**:** Packing L1

Analytical: 4.6-mm × 15-cm; packing L1

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 20–50 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[Note—The relative retention times for clarithromycin and clarithromycin related compound A are about 0.75 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between clarithromycin and clarithromycin related compound A, *System suitability solution*

Tailing factor: 0.9–1.5, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) in the portion of Tablets taken:

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 clarithromycin in the *Standard solution* (µg/mL)

C_U = nominal concentration of clarithromycin in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Buffer B: Dissolve 816.5 g of monobasic potassium phosphate and 48 g of sodium hydroxide in about 4 L of water, mix, and dilute with water to 20 L. Adjust with either concentrated phosphoric acid or 1 N sodium hydroxide to a pH of 6.0 ± 0.05.

Medium: *Buffer B*; 900 mL

Apparatus 2: 75 rpm

Times: 30, 45, 60, and 120 min

Standard solutions: Prepare five solutions of USP Clarithromycin RS dissolved in acetonitrile and diluted with *Medium*, with known concentrations over a range of about 60–600 µg/mL.

Sample solution: Use portions of the solution under test passed through a polyethylene filter of 35-µm pore size.

Chromatographic system: Proceed as directed in the *Assay*, except for the *Injection volume*.

Injection volume: 50 µL

Analysis

Samples: *Standard solutions* and *Sample solution*

Perform a linear regression analysis to generate a standard curve using the peak area of each *Standard solution* versus its concentration. Determine the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each specified time interval, using the peak area of each *Sample solution* and the linear regression statistics for the *Standard solutions*.

Tolerances: The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Table 1*.

Table 1

Level	Time (min)	Amount Dissolved, Individual Limits (%)	Amount Dissolved, Average Limits (%)
L1	30	NMT 65	—
	45	55–85	—
	60	NLT 75	—
	120	NLT 85	—
L2	30	NMT 75	NMT 65
	45	45–95	55–85
	60	NLT 65	NLT 75
	120	NLT 75	NLT 85

Level	Time (min)	Amount Dissolved, Individual Limits (%)	Amount Dissolved, Average Limits (%)
	30	NMT 2 Tablets release more than 75%, and no individual Tablet releases more than 85%	NMT 65
	45	NMT 2 Tablets are outside the range of 45%–95%, and no individual Tablet is outside the range of 35%–105%	55–85
	60	NMT 2 Tablets release less than 65%, and no individual Tablet releases less than 55%	NLT 75
L3	120	NMT 2 Tablets release less than 75%, and no individual Tablet releases less than 65%	NLT 85

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Buffer C: 0.05 M phosphate buffer with a pH of 6.8, containing 0.5% of sodium lauryl sulfate

Buffer D: 9.2 g/L of monobasic sodium phosphate monohydrate in water; adjusted with phosphoric acid to a pH of 2.5 prior to final dilution

Medium: *Buffer C*; 900 mL, degassed by sonication and vacuum

Apparatus 1: 100 rpm

Times: 2, 12, and 24 h

Mobile phase: Methanol and *Buffer D* (65:35)

Standard solution: 0.56 mg/mL of USP Clarithromycin RS in a solution of methanol and *Medium* (1 in 10). Dissolve first in methanol using 10% of the final volume, and dilute with *Medium* to volume.

Sample solution: Centrifuge the solution under test at 2500 rpm for 10 min.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point (Q_T):

$$Q_2 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_{12} = [Q_2 \times (V_S/V)] + [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100]$$

$$Q_{24} = [Q_2 \times (V_S/V)] + [Q_{12} \times V_S/(V - 2V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100]$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of clarithromycin in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

V_S = volume of the sample withdrawn at each time point (mL)

Tolerances: See *Table 2*.

Table 2

Time (h)	Amount Dissolved (%)
2	NMT 20
12	45–70
24	NLT 80

The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Buffer E: Dissolve 3.59 g of sodium acetate trihydrate and 11.0 mL of 2 N acetic acid in 1000 mL of water. Adjust with 2 N acetic acid to a pH of 4.75.

Buffer F: 9.12 g/L of monobasic potassium phosphate in water

Medium: *Buffer E*; 1000 mL

Apparatus 1: 10 mesh; 50 rpm

Times: 1, 2, 4, 8, and 12 h

Mobile phase: Methanol and *Buffer F* (65:35). Adjust with phosphoric acid to a pH of 4.0.

Standard stock solution: 625 µg/mL of clarithromycin from USP Clarithromycin RS in methanol. Shake and sonicate, if necessary, to dissolve.

Standard solution: 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*

System suitability stock solution: 625 µg/mL of USP Clarithromycin Related Compound A RS in methanol

System suitability solution: 125 µg/mL of clarithromycin related compound A from *System suitability stock solution* and 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*

Sample solution: Withdraw 10 mL of the solution under test from each vessel and replace with 10 mL of *Medium*. Transfer 3 mL of the withdrawn solution to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass through a filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[NOTE—The relative retention times for clarithromycin and clarithromycin related compound A are about 0.75 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between clarithromycin and clarithromycin related compound A, *System suitability solution*

Tailing factor: 0.9–2, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point (Q_T):

$$Q_1 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_2 = [Q_1 \times (V_S/V)] + [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100]$$

$$Q_4 = [Q_1 \times (V_S/V)] + [Q_2 \times V_S/(V - 2V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100]$$

$$Q_8 = [Q_1 \times (V_S/V)] + [Q_2 \times V_S/(V - 2V_S)] + [Q_4 \times V_S/(V - 3V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 3V_S) \times 100]$$

$$Q_{12} = [Q_1 \times (V_S/V)] + [Q_2 \times V_S/(V - 2V_S)] + [Q_4 \times V_S/(V - 3V_S)] + [Q_8 \times V_S/(V - 4V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 4V_S) \times 100]$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of clarithromycin in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 1000 mL

V_S = volume of the sample withdrawn at each time point (mL)

Tolerances: See *Table 3*.

Table 3

Time (h)	Amount Dissolved (%)
1	NMT 15
2	10–30
4	35–55
8	NLT 80
12	NLT 90

The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Buffer G: 6.8 g/L of monobasic potassium phosphate and 0.18 g/L of sodium hydroxide in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 6.0 ± 0.1.

Buffer H: 6.8 g/L of monobasic potassium phosphate in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 4.5 ± 0.1.

Medium: *Buffer G*; 900 mL

Apparatus 2: 50 rpm

Times: 2, 4, 8, and 12 h

Mobile phase: Methanol and *Buffer H* (64:36)

Standard solution: 0.4 mg/mL of USP Clarithromycin RS in methanol and *Medium* (4:96). Dissolve first in *Medium*, using 60% of the final volume. Sonicate about 10 min until dissolved. Add methanol, using 4% of the final volume. Dilute with *Medium* to volume.

Sample solution: Use the solution under test, passed through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 203 nm

Column: 4.0-mm × 12.5-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the concentration, in mg/mL, of clarithromycin ($C_{38}H_{69}NO_{13}$) in the *Sample solution* at each time point (Q_T):

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point (Q_T):

$$Q_2 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_4 = [Q_2 \times (V_S/V)] + [(r_U/r_S) \times (C_S/L) \times (V - V_S) \times 100]$$

$$Q_8 = [Q_2 \times (V_S/V)] + [Q_4 \times V_S/(V - 2V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 2V_S) \times 100]$$

$$Q_{12} = [Q_2 \times (V_S/V)] + [Q_4 \times V_S/(V - 2V_S)] + [Q_8 \times V_S/(V - 3V_S)] + [(r_U/r_S) \times (C_S/L) \times (V - 3V_S) \times 100]$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of clarithromycin in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

V_S = volume of the sample withdrawn at each time point (mL)

Tolerances: See *Table 4*.

Table 4

Time (h)	Amount Dissolved (%)
2	NMT 25
4	20–40
8	45–75
12	NLT 80

The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: Phosphate buffer, pH 6.0 (6.8 g/L of monobasic potassium phosphate and 0.18 g/L of sodium hydroxide in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 6.0 ± 0.1.); 900 mL

Apparatus 2: 50 rpm, with sinker (see *Dissolution ⟨711⟩, Figure 2a*)

Times: 2, 4, 8, and 14 h

Buffer: 9.11 g/L of monobasic potassium phosphate in water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 2.5 ± 0.05.

Mobile phase: Acetonitrile and *Buffer* (55:45)

Standard solution: 0.55 mg/mL of USP Clarithromycin RS in *Medium*. Sonicate to dissolve prior to dilution to final volume.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.22-µm pore size. Replace the portion of solution withdrawn with an equal volume of *Medium*.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 2.1-mm × 10-cm; 1.7-µm packing L1

Column temperature: 50°

Flow rate: 0.25 mL/min

Injection volume: 2 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of clarithromycin ($C_{38}H_{69}NO_{13}$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of clarithromycin in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 25
2	4	20–40
3	8	45–75
4	14	NLT 80

The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 6:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: 0.05 M sodium phosphate buffer, pH 6.8 with 5 g/L of sodium dodecyl sulfate, prepared as follows. Dissolve 38.3 g of sodium phosphate, tribasic in 100 mL of water and transfer to a 2-L container containing 1800 mL of water. Add 12.5 mL of hydrochloric acid and adjust with sodium hydroxide or hydrochloric acid to a pH of 6.8. Dilute with water to volume. To each liter of this solution, add 5 g of sodium dodecyl sulfate and dissolve by stirring NLT 20 min; 900 mL, deaerated.

Apparatus 1: 100 rpm

Times: 2, 12, and 24 h

Buffer: Dissolve 9.2 g of sodium phosphate, monobasic in 860 mL of water, and adjust with phosphoric acid to a pH of 2.5. Dilute with water to 1000 mL.

Mobile phase: Methanol and *Buffer* (65:35)

Standard solution: 0.56 mg/mL of USP Clarithromycin RS prepared as follows. Transfer an appropriate quantity of USP Clarithromycin RS to a suitable volumetric flask. Add 10% of the flask volume of methanol and sonicate to dissolve, if necessary. Dilute with *Medium* to volume.

Sample solution: Centrifuge a portion of the solution under test and use the supernatant. [NOTE—The use of a centrifuge speed at 2500 rpm for 10 min may be suitable.]

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 5 µL

Run time: NLT 1.7 times the retention time of clarithromycin

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Tailing factor: NMT 2.0

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of clarithromycin ($C_{38}H_{69}NO_{13}$) in the sample withdrawn from the vessel at each time point (*i*):

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

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

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

C_S = concentration of USP Clarithromycin RS from the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of clarithromycin in the portion of sample withdrawn at the specified time point *i* (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point from the *Medium* (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 20
2	12	50–75
3	24	NLT 80

The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-Dec-2023)

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

Solution A: 4.76 g/L of monobasic potassium phosphate in water. Adjust with dilute phosphoric acid or potassium hydroxide to a pH of 4.4 ± 0.05.

Solution B: Acetonitrile

Mobile phase: See ▲*Table 7*.

Table 7▲ (RB 1-Dec-2023)

Time (min)	Solution A (%)	Solution B (%)
0	75	25
32	40	60
34	40	60
36	75	25
45	75	25

Diluent: Acetonitrile and water (50:50)

System suitability solution: 3.0 mg/mL of USP Clarithromycin Identity RS in acetonitrile and water (1:1). Dissolve first in acetonitrile, using 50% of the final volume, sonicate, and dilute with water to volume. Pass this solution through a suitable filter of 0.45-µm pore size.

Standard stock solution: 0.38 mg/mL of USP Clarithromycin RS in acetonitrile and water (1:1). Dissolve first in acetonitrile, using 50% of the final volume, sonicate in cool water to dissolve it completely, and dilute with water to volume.

Standard solution: 0.015 mg/mL of USP Clarithromycin RS from *Standard stock solution* in *Diluent*. Pass this solution through a suitable filter of 0.45-µm pore size. Store this solution at 10° and discard after 24 h.

Sensitivity solution: 0.003 mg/mL of USP Clarithromycin RS from *Standard solution* in *Diluent.* Store this solution at 10° and discard after 24 h.

Sample solution: Nominally 3.0 mg/mL of clarithromycin from NLT 20 Tablets prepared as follows. Transfer a portion of the finely powdered Tablets, equivalent to 300 mg of clarithromycin, to a 100-mL volumetric flask containing 25 mL of acetonitrile. Add another 25 mL of acetonitrile and sonicate for about 10 min in cool water. Then add 25 mL of water, sonicate for about 2 min, and dilute with water to volume. Pass through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate. Store this solution at 10° and discard after 24 h.

Chromatographic system

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

Mode: LC

Detector: UV 205 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Temperatures

Autosampler: 10°

Column: 40°

Flow rate: 1.1 mL/min

Injection volume: 10 µL

Run time: NLT 3 times the retention time of clarithromycin

System suitability

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

[NOTE—See ▲*Table 8*▲ (RB 1-Dec-2023) for relative retention times.]

Suitability requirements

Peak-to-valley ratio: NLT 3.0 between clarithromycin and clarithromycin impurity D, *System suitability solution*

Calculate the *Peak-to-valley ratio* as follows:

$$\text{Result} = H_P/H_V$$

H_P = height above the baseline of the clarithromycin impurity D peak

H_V = height above the baseline of the lowest point of the curve separating the clarithromycin impurity D peak from the clarithromycin peak

Tailing factor: NMT 2.5, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

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

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

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

F = relative response factor (see ▲*Table 8*▲ (RB 1-Dec-2023))

Acceptance criteria: See ▲*Table 8*.▲ (RB 1-Dec-2023) Not more than four impurities exceed 0.4%. The reporting threshold is 0.1%. Disregard the peaks eluting before impurity I and after impurity H.

▲Table 8▲ (RB 1-Dec-2023)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Clarithromycin impurity I[a]	0.47	1.0	1.0
Clarithromycin impurity A (clarithromycin F)[b,c]	0.51	—	—
Clarithromycin impurity C[d]	0.92	3.0	0.70
Clarithromycin impurity D[e]	0.98	1.0	0.70
Clarithromycin	1.0	—	—
Clarithromycin related compound A[f]	1.25	1.0	0.70
Clarithromycin impurity F[g,c]	1.33	—	—
Clarithromycin impurity G[h]	1.64	4.4	0.70
Clarithromycin impurity H[i,c]	1.80	—	—
Any other individual impurity	—	1.0	0.2
Total impurities	—	—	2.5

[a] 3-*O*-Decladinosyl-6-*O*-methylerythromycin A.

[b] 2-Demethyl-2-(hydroxymethyl)-6-*O*-methylerythromycin A.

[c] Process impurities that are controlled in the drug substance are not to be reported. They are not to be included in total impurities. They are listed here for information only.

[d] 6-*O*-Methylerythromycin A (*E*)-9-oxime.

[e] 3"-*N*-Demethyl-6-*O*-methylerythromycin A.

[f] 6,11-Di-*O*-methylerythromycin A.

[g] 6,12-Di-*O*-methylerythromycin A.

[h] 6-*O*-Methylerythromycin A (*E*)-9-(*O*-methyloxime).

[i] 3"-*N*-Demethyl-3'-*N*-formyl-6-*O*-methylerythromycin A.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, protected from light. Store at 25°, excursions permitted between 15° and 30°.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Clarithromycin RS

USP Clarithromycin Related Compound A RS

6,11-Di-*O*-methylerythromycin A.

$C_{39}H_{71}NO_{13}$ 762.00

USP Clarithromycin Identity RS

Contains a mixture of other impurities and the following:
Clarithromycin.
Clarithromycin impurity D;
3"-*N*-Demethyl-6-*O*-methylerythromycin A.

$C_{37}H_{67}NO_{13}$ 733.93

Topic/Question	Contact	Expert Committee
CLARITHROMYCIN EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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