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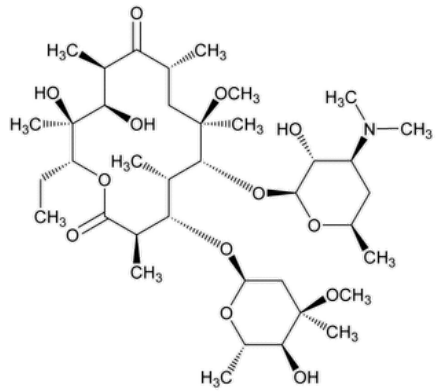
# Clarithromycin



$C_{38}H_{69}NO_{13}$ 747.95

Erythromycin, 6-*O*-methyl-;

6-*O*-Methylerythromycin CAS RN®: 81103-11-9; UNII: H1250JIK0A.

## DEFINITION

Clarithromycin contains NLT 96.0% and NMT 102.0% of clarithromycin ($C_{38}H_{69}NO_{13}$), calculated on the anhydrous basis.

## IDENTIFICATION

***Change to read:***

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of *Standard solution 1*, as obtained in the *Assay*.

## ASSAY

• **Procedure**

**Solution A, Solution B, Mobile phase, Diluent, Standard solution 1, Standard solution 2, Standard solution 4, Sample solution,** and

**Chromatographic system:** Proceed as directed in *Organic Impurities*.

**System suitability**

**Samples:** *Standard solution 1*, *Standard solution 2*, and *Standard solution 4*

[Note—See the relative retention times in *Table 2*. The typical retention time for clarithromycin is about 11 min.]

**Suitability requirements**

**Peak-to-valley ratio:** NLT 3.0, *Standard solution 4*

The *Peak-to-valley ratio* is calculated as follows:

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

$H_P$ = height above the baseline of the clarithromycin impurity D peak, *Standard solution 4*

$H_V$ = height above the baseline of the lowest point of the curve separating the clarithromycin impurity D peak from the clarithromycin peak, *Standard solution 4*

**Tailing factor:** NMT 1.7, *Standard solution 2*

**Relative standard deviation:** NMT 1.5%, *Standard solution 1*

**Analysis**

**Samples:** *Standard solution 1* and *Sample solution*

Calculate the percentage of clarithromycin ($C_{38}H_{69}NO_{13}$) in the portion of Clarithromycin 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 *Standard solution 1*

$C_S$ = concentration of USP Clarithromycin RS in *Standard solution 1* (mg/mL)

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

**Acceptance criteria:** 96.0%–102.0% on the anhydrous basis

## IMPURITIES

- **Residue on Ignition ⟨281⟩**

**Sample:** 0.5 g

**Acceptance criteria:** NMT 0.2%

- **Organic Impurities**

**Solution A:** 4.76 g/L of monobasic potassium phosphate. Adjust with dilute phosphoric acid (1 in 10) or potassium hydroxide (45% w/v) to a pH of 4.4. Pass this solution through a C18 filtration kit.

**Solution B:** Acetonitrile

**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 75 | 25 |
| 32 | 40 | 60 |
| 34 | 40 | 60 |
| 36 | 75 | 25 |
| 42 | 75 | 25 |

**Diluent:** Acetonitrile and *water* (1:1)

**Standard solution 1:** 1.5 mg/mL of USP Clarithromycin RS in acetonitrile and *water* (1:1). Dissolve first in acetonitrile, using 50% of the final volume, and dilute with *water* to volume.

**Standard solution 2:** 75 µg/mL of USP Clarithromycin RS from *Standard solution 1* in *Diluent*

**Standard solution 3:** 7.5 µg/mL of USP Clarithromycin RS from *Standard solution 2* in *Diluent*

**Standard solution 4:** 1.5 mg/mL of USP Clarithromycin Identity RS in acetonitrile and *water* (1:1). Dissolve first in acetonitrile, using 50% of the final volume, and dilute with *water* to volume.

**Sample solution:** 1.5 mg/mL of Clarithromycin in acetonitrile and *water* (1:1). Dissolve first in acetonitrile, using 50% of the final volume, and dilute with water to volume.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 205 nm

**Column:** 4.6-mm × 10-cm; packing L1

**Column temperature:** 40°

**Flow rate:** 1.1 mL/min

**Injection volume:** 10 µL

**System suitability**

**Samples:** *Standard solution 2* and *Standard solution 4*

[Note—See the relative retention times in *Table 2*. The typical retention time for clarithromycin is about 11 min.]

**Suitability requirements**

**Peak-to-valley ratio:** NLT 3.0, *Standard solution 4*

The *Peak-to-valley ratio* is calculated as follows:

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

$H_P$ = height above the baseline of the clarithromycin impurity D peak, *Standard solution 4*

$H_V$ = height above the baseline of the lowest point of the curve separating the clarithromycin impurity D peak from the clarithromycin peak, *Standard solution 4*

**Tailing factor:** NMT 1.7, *Standard solution 2*

**Analysis**

**Samples:** *Diluent*, *Standard solution 2*, *Standard solution 3*, *Standard solution 4*, and *Sample solution*

Calculate the percentage of each impurity in the portion of Clarithromycin taken:

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

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

$r_S$ = peak response of clarithromycin from *Standard solution 3*

$C_S$ = concentration of USP Clarithromycin RS in *Standard solution 3* (mg/mL)

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

$F$ = relative response factor (see *Table 2*)

**Acceptance criteria:** The reporting threshold is 0.1%. Disregard the peaks eluting before impurity I and after impurity H.

**Any individual impurity:** NMT 1.0%. NMT four impurities exceed 0.4%.

**Total impurities:** NMT 3.5%

**Table 2**

| Name | Relative Retention Time | Relative Response Factor |
|---|---|---|
| Clarithromycin impurity I[a] | 0.38 | 1.0 |
| Clarithromycin impurity A[b] (clarithromycin F) | 0.42 | 1.0 |
| Clarithromycin impurity J[c] | 0.63 | 1.0 |
| Clarithromycin impurity L[d] | 0.74 | 1.0 |
| Clarithromycin impurity B[e] | 0.79 | 1.0 |
| Clarithromycin impurity M[f] | 0.81 | 1.0 |
| Clarithromycin impurity C[g] | 0.89 | 1.0 |
| Clarithromycin impurity D[h] | 0.96 | 1.0 |
| Clarithromycin | 1.0 | — |
| Clarithromycin impurity N[i] | 1.15 | 1.0 |

| Name | Relative Retention Time | Relative Response Factor |
|---|---|---|
| Clarithromycin related compound A[j] | 1.27 | 1.0 |
| Clarithromycin impurity F[k] | 1.33 | 1.0 |
| Clarithromycin impurity P[l] | 1.35 | 1.0 |
| Clarithromycin impurity O[m] | 1.38 | 1.0 |
| Clarithromycin impurity K[n] | 1.59 | 1.0 |
| Clarithromycin impurity G[o] | 1.72 | 3.7 |
| Clarithromycin impurity H[p] | 1.82 | 6.7 |

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

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

[c] Erythromycin A (*E*)-9-oxime.

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

[e] 6-*O*-Methyl-15-norerythromycin A.

[f] 3"-*N*-Demethyl-6-*O*-methylerythromycin A (*E*)-9-oxime.

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

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

[i] (10*E*)-10,11-Didehydro-11-deoxy-6-*O*-methylerythromycin A.

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

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

[l] 4',6-Di-*O*-methylerythromycin A.

[m] 6-*O*-Methylerythromycin A (*Z*)-9-(*O*-methyloxime).

[n] (1*S*,2*R*,5*R*,6*S*,7*S*,8*R*,9*R*,11*Z*)-2-Ethyl-6-hydroxy-9-methoxy-1,5,7,9,11,13-hexamethyl-8-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexapyranosyl]oxy]-3,15-dioxabicyclo[10.2.1]pentadeca-11,13-dien-4-one (3-*O*-decladinosyl-8,9:10,11-dianhydro-6-*O*-methylerythromycin A)-9,12-hemiketal.

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

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

## SPECIFIC TESTS

- **Optical Rotation ⟨781S⟩, *Procedures, Specific Rotation***
  **Sample solution:** 10 mg/mL in methylene chloride
  **Acceptance criteria:** −94° to −102° (at 20°)
- **Crystallinity ⟨695⟩:** Meets the requirements
- **pH ⟨791⟩**
  **Sample:** 2-mg/mL suspension in methanol and *water* (1:19)
  **Acceptance criteria:** 8.0–10.0
- **Water Determination ⟨921⟩, *Method I*:** NMT 2.0%

## ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- **USP Reference Standards ⟨11⟩**
  USP Clarithromycin RS
  USP Clarithromycin Identity RS

This is a mixture of clarithromycin, clarithromycin impurity D (3"-*N*-demethyl-6-*O*-methylerythromycin A; $C_{37}H_{67}NO_{13}$; 733.9), and other impurities.

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

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| CLARITHROMYCIN | Documentary Standards Support | SM12020 Small Molecules 1 |

**Chromatographic Database Information:** Chromatographic Database

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