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Clarithromycin Prolonged-release Tablets

General Notices

Prolonged-release Clarithromycin Tablets

Details for the public consultation of this monograph are as follows:

EAG AIM	**Anti-infective Medicines**
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Deadline for Comment	31st March 2026
Target Publication (subject to change)	BP 2027
Notes:	**REVISED** Related Substances and Assay updated If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Macrolide antibacterial.

Clarithromycin Prolonged-release Tablets from different manufacturers, whilst complying with the requirements of the monograph, are not interchangeable unless otherwise justified and authorised.

DEFINITION

Clarithromycin Prolonged-release Tablets contain *Clarithromycin*. They are formulated so that the medicament is released over a period of several hours.

PRODUCTION

A suitable dissolution test is carried out to demonstrate the appropriate release of Clarithromycin. The dissolution profile reflects the *in vivo* performance which in turn is compatible with the dosage schedule recommended by the manufacturer.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of clarithromycin, $C_{38}H_{69}NO_{13}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

Shake a quantity of the powdered tablets containing 0.5 g of Clarithromycin with 10 mL of *water* and extract with 20 mL of *dichloromethane*. Separate the lower dichloromethane layer and centrifuge. Filter the supernatant liquid through a GF/C filter paper (Whatman GF/C is suitable) and through a 0.45-µm PTFE filter. Evaporate the filtrate to dryness under a stream of nitrogen and dry the residue under vacuum for 2 hours. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with *reference spectrum A* of clarithromycin *(RS 424)*.

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

Solution A: 10 volumes mobile phase B and 90 volumes mobile phase A.

(1) Disperse a quantity of powdered tablets containing 75 mg of Clarithromycin in 25 mL of acetonitrile R1 with the aid of ultrasound, dilute to 50 mL with *water*. Filter through a Whatman GF/C filter and then through a 0.45-µm PTFE filter.
(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.
(3) Dissolve 3 mg of *clarithromycin for peak identification EPCRS* in 1 mL of *acetonitrile R1* and dilute to 2 mL with *water*.
(4) Dilute 1 volume of solution (2) to 10 volumes with solution A.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 2.1 mm) packed with *end-capped polar-embedded octadecylsilyl silica gel for chromatography* (1.7 µm) (Acquity UPLC BEH Shield RP18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 205 nm.
(f) Inject 3 µL of each solution.

MOBILE PHASE

Mobile phase A 100 volumes of 0.1M *potassium dihydrogen orthophosphate* adjusted to pH 7.0 with *disodium hydrogen orthophosphate, anhydrous*, 200 volumes of *acetonitrile R1* and 700 volumes of *water*.

Mobile phase B 100 volumes of 0.1M *potassium dihydrogen orthophosphate* adjusted to pH 7.0 with disodium hydrogen orthophosphate, anhydrous, 350 volumes of *water* and 550 volumes of

acetonitrile R1.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-1	95	5	isocratic
1-9	95→10	5→90	linear gradient
9-13	10	90	isocratic
13-14	10→95	90→5	linear gradient
14-15	95	5	re-equilibration

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity F and impurity H is between 3 and 8 inclusive. Signal to noise ratio for solution (4): at least 10.

CALCULATION OF IMPURITIES

For each impurity, use the concentration of clarithromycin in solution (2).

For the reporting threshold, use the concentration of clarithromycin in solution (4).

For peak identification, use solution (3).

Clarithromycin retention time: about 6 minutes.

Relative retention: impurity I, about 0.5; impurity A, about 0.6; impurity L, about 0.85; impurity D, about 0.87; impurity 1, about 0.92; impurity E, about 1.11; impurity F, about 1.15; impurity H, about 1.3; impurity K, about 1.4 and impurity G, about 1.5.

Correction factors: impurities K, N and 1, multiply by 0.2, 0.4, and 1.3 respectively.

LIMITS

- no more than 4 impurities: not more than 1.0%;

- any other impurity: not more than 0.4%;

- total impurities: not more than 3.5%;

- reporting threshold: 0.1%.

Disregard any peaks eluting before impurity I and after impurity G.

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Weigh and powder 20 tablets. To a quantity of powdered tablets containing 2 g of Clarithromycin add 350 mL of *methanol*. Mix with the aid of ultrasound for 15 minutes, shake vigorously for 15 minutes and allow to cool. Add sufficient *methanol* to produce 500 mL and filter the suspension (Whatman GF/C filter paper is suitable). Dilute 1 volume of the filtrate to 40 volumes with the mobile phase and filter through a 0.45-µm filter.
(2) 0.01% w/v of *clarithromycin BPCRS* in the mobile phase.
(3) 0.01% w/v of each of *clarithromycin BPCRS* and *clarithromycin for peak identification EPCRS* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Superspher ODS2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use a column temperature of 50°.
(e) Use a detection wavelength of 210 nm.
(f) Inject 50 µL of each solution.

MOBILE PHASE

35 volumes of 0.067M *potassium dihydrogen orthophosphate* and 65 volumes of *methanol R1* adjusted to pH 4.0 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions the approximate retention times for clarithromycin and clarithromycin impurity E are 4 and 6 minutes respectively.

DETERMINATION OF CONTENT

Calculate the content of $C_{38}H_{69}NO_{13}$ in the tablets using the declared content of $C_{38}H_{69}NO_{13}$ in *clarithromycin BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, D, E, F, G, H, I, K, L, N and P listed under Clarithromycin and;

1. 6-*O*-methyl-erythromycin A-*N*-oxide