Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

Clarithromycin Prolonged-release Tablets

Published on: 08.10.2024 **Last date for comments:** 22.11.2024

This draft proposal contains monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

Description	**Details**
Document version	2.0
Monograph proposed for inclusion	IP 2026
Tentative effective date of monograph	January, 2026
First draft published on IPC website for public comments	11.09.2023
Draft revision published on IPC website for public comments	08.10.2024
Further follow-up action as required.	

Clarithromycin Prolonged-release Tablets

Clarithromycin Sustained-release Tablets; Clarithromycin Extended-release Tablets

Clarithromycin Prolonged-release Tablets contains not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of clarithromycin, $C_{38}H_{69}NO_{13}$.

Usual strengths. 250 mg; 500 mg.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (a).

Tests

Dissolution (2.5.2).

Apparatus No. 2 (Paddle),
Medium. 900 ml of buffer solution prepared by dissolving 40.8 g of *potassium dihydrogen phosphate* and 2.4 g of *sodium hydroxide* in 1000 ml of *water*, adjusted to pH 6.0 with *orthophosphoric acid* or*1M sodium hydroxide*.
Speed and time. 75 rpm and 30 minutes, 45 minutes, 60 minutes and120 minutes.

Withdraw a suitable volume of the medium and filter through a membrane filter.

Test solution: Use the filtrate, dilute if ~~necessary~~necessary, with the dissolution medium.

Reference solution. Dissolve a suitable quantity of *clarithromycin IPRS* in *acetonitrile*, and dilute with the dissolution medium to obtain a solution having a known concentration similar to the test solution.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm), (Such as Nucleosil C18),
- column temperature: 50°,
- mobile phase. A mixture of 35 volumes of *0.067 M potassium dihydrogen phosphate* and 65 volumes of *methanol*, adjusted to pH 4.0 with *orthophosphoric acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 50 µl.

Inject the reference solution and the test solution.

Calculate the content of $C_{38}H_{69}NO_{13}$ in tablets.

The percentages of the labelled amount of clarithromycin, $C_{38}H_{69}NO_{13}$ dissolved at the times specified conform to 2.5.2 Dissolution test, Prolonged-release dosage forms-Table 2.

At 30 minutes, not more than 65 per cent; at 45 minutes, not less than 55 per cent and not more than 85 per cent; at 60 minutes, not less than 75 per cent and at 120 minutes, not less than 85 per cent.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Use freshly prepared solutions at 10°and store protected from light ~~at 10°.~~

Solvent mixture. Equal volumes of *acetonitrile* and *water*.

Test solution. Disperse a quantity of the powdered tablets containing 0.3 g of Clarithromycin in 50 ml of *acetonitrile* with the aid of ultrasound for 10 minutes then add 25 ml of *water*, sonicate for 2 minutes and dilute to 100.0 ml with *water*, filter.

Reference solution (a). Dissolve 15 mg of *clarithromycin IPRS* in 25 ml of *acetonitrile* with the aid of ultrasound and dilute to 50.0 ml with the *water*. Dilute 5.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A 0.3 per cent w/v solution of *clarithromycin identity IPRS* in *acetonitrile* and *water* (1:1) prepared by dissolving first in *acetonitrile* (50 per cent of final volume), sonicate and dilute to volume with *water*.

Reference solution (c). Dilute 5.0 ml of rReference solution (a) to 25.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with end capped octyladecylsilane bonded to porous silica (3.5 µm), (Such as Kromasil 100 C-18)
- sample temperature: 10°,
- column temperature: 40°,
- mobile phase. A. a buffer solution prepared by dissolving 4.76 g of *potassium dihydrogen phosphate* in 1000 ml of *water*, adjusted to pH 4.4 with *orthophosphoric acid* or *potassium hydroxide*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.1 ml per minute,
- spectrophotometer set at 205 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	75	25
32	40	60
34	40	60
36	75	25
45	75	25

Name	Relative retention time	Correction factor
Clarithromycin impurity I[1]	0.47	---
Clarithromycin impurity A[2*]	0.51	---
Clarithromycin impurity C[3]	0.92	0.33
Clarithromycin impurity D[4]	0.98	---
Clarithromycin	1.0	---
Clarithromycin impurity E[5]	1.25	---
Clarithromycin impurity F[6 *]	1.33	---
Clarithromycin impurity G[7]	1.64	0.23
Clarithromycin impurity H[8*]	1.80	---

Note- Not more than four impurities exceed 0.4 per cent.
* Process impurity, included for information only and not to be included in total degradation products,
[1]3-*O*-decladinosyl-6-*O*-methylerythromycin A,
[2]2-Demethyl-2-(hydroxymethyl)-6-*O*- methylerythromycin A, (Clarithromycin F)
[3]6-*O*-methylerythromycin A (*E*)-9-oxime,
[4]3"-*N*-demethyl-6-*O*-methylerythromycin A,
[5]6,11-Di-O-methylerythromycin A.
[6]6,12-di-*O*-methylerythromycin A,
[7]6-*O*-methylerythromycin A (*E*)-9-(*O*-methyloxime),
[8]3"-*N*-demethyl-3'-*N*-formyl-6-*O*-methylerythromycin A

Inject reference solution (a), (b) and (c). The test is not valid unless the peak-to-valley ratio (*Hp/Hv*) is not less than 3.0, where *Hp* height above the baseline of the peak due to clarithromycin impurity D and *Hv* is the height above the baseline of the lowest point of the curve separating the peak due to clarithromycin impurity D from the peak due to clarithromycin in the chromatogram obtained with reference solution (b), the tailing factor is not more than 2.5, the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal–to–noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the area of any peak corresponding to clarithromycin impurity I is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any peak corresponding to clarithromycin impurity C, clarithromycin impurity D, clarithromycin impurity E and clarithromycin impurity G, each of, is not more than 1.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.7 per cent), the area of any other secondary peak is

not more than 0.4 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (2.5 per cent). Ignore the peaks eluting before clarithromycin impurity I and after clarithromycin impurity H, and with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

NOTE — Use freshly prepared solutions at 10°and store protected from light
~~*Note: Protect the solutions from light and store at 10°.*~~

Test solution. Weigh and powder 20 tablets. Transfer a quantity of the powder~~ed tablets~~ containing 2.0 g of Clarithromycin to a 500-ml volumetric flask, add 350 ml of *methanol* and shake by mechanical means for 30 minutes and dilute to volume with *methanol*, sonicate for 30 minutes and allow to stand for at least 16 hours, mix, allow any insoluble matter to settle. Dilute 3.0 ml of supernatant to 100.0 ml with the mobile phase, filter.

Reference solution (a). A 0.0625 per cent w/v solution of *clarithromycin IPRS* in *methanol*. Dilute 2.0 ml of the solution to 10.0 ml with the mobile phase.

Reference solution (b). A 0.0625 per cent w/v solution of *clarithromycin impurity E IPRS* in *methanol*. Transfer 2.0 ml of the solution to a 10-ml volumetric flask, add 2.0 ml of reference solution (a) and dilute to volume with the mobile phase.

Use chromatographic system as described under Dissolution.

The relative retention time with reference to clarithromycin impurity E, for clarithromycin is about 0.75.

Inject reference solution (a) and (b). The test is not valid unless the resolution between clarithromycin and clarithromycin impurity E is not less than 2.0 in the chromatogram obtained with reference solution (b), the tailing factor is not less than 0.9 and not more than 1.5 and the relative standard deviation for replicate injection is not more than 2.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{38}H_{69}NO_{13}$ in tablets.

Storage. Store protected from light, at a temperature not exceeding 30^0.