Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

Nilotinib Capsules

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This draft proposal contains general chapter 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. 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

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Further follow-up action as required.	

Nilotinib Capsules

Nilotinib Hydrochloride Capsules

Nilotinib Capsules contain Nilotinib Hydrochloride Monohydrate equivalent to not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Nilotinib, $C_{28}H_{22}F_3N_7O$.

Usual strengths. 150 mg; 200 mg.

CAUTION — Nilotinib hydrochloride is cytotoxic, extra care required to prevent inhaling particles and exposing the skin to it.

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 (b).

Tests

Dissolution (2.5.2).

Apparatus No. 1 (Basket),
Medium. 1000 ml of *0.1 M hydrochloric acid,*
Speed and time. 100 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, dilute suitably, if necessary, with the medium, at the maximum at about 260 nm (2.4.7), using 0.1 cm quartz cell. Calculate the content of $C_{28}H_{22}F_3N_7O$ in the medium from the absorbance obtained from a solution of known concentration of *nilotinib hydrochloride monohydrate IPRS* in the dissolution medium.

Q. Not less than 75 per cent of the stated amount of $C_{28}H_{22}F_3N_7O$.

Nilotinib impurity A. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light.

Solvent mixture. 20 volumes of *dimethyl sulphoxide* and 80 volumes of *water.*

Test solution. Disperse a quantity of the mixed content of the capsules containing 1.2 g of Nilotinib to a 20-ml volumetric flask, add 4 ml of *dimethyl sulphoxide*, stir on a magnetic stirrer for 10 minutes, add 12 ml of *water*, allow to equilibrate at room temperature without shaking to avoid foam formation and dilute to volume with the *water*. Shake well and stir on a magnetic stirrer for 5 minutes and allow to stand for 4 hours in the dark to precipitate. Filter the supernatant through 0.45 µm filter.

Reference solution. A 0.0075 per cent w/v solution of *nilotinib impurity A IPRS* [3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)aniline] in *dimethyl sulphoxide*. Dilute 1.0 ml of the solution to 100.0 ml with *dimethyl sulphoxide*. Dilute 4.0 ml of reference solution (a) to 20.0 ml with *water*.

Chromatographic system
- a stainless steel column 15 cm × 3.0 mm, packed with octadecylsilane bonded to spherical silica (3 µm) (such as ProntoSIL,120-3-C18-ace-EPS),
- column temperature: 40°,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, adjusted to pH 3.0 with *orthophosphoric acid*,
  B. a mixture of 20 volumes of mobile phase A and 80 volumes of *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 207 nm,

– injection volume: 20 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	85	15
8	80	20
10	75	25
16	10	90
17	10	90
17.1	85	15
20	85	15

Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 10.0 per cent.

Inject the reference solution and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to nilotinib impurity A is not more than 2.4 times the area of the principal peak in the chromatogram obtained with the reference solution (6 ppm).

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light.

Solvent mixture. Equal volumes of *water* and *ethanol (95 per cent)*.

Test solution. Weigh and mix the content of 20 capsules. Disperse a quantity of the mixed content containing 0.5 g of nilotinib in *ethanol (95 per cent)*, with the aid of magnetic stirrer for 30 minutes, sonicate for 10 minutes, stir again for 30 minutes and dilute to 500.0 ml with *ethanol (95 per cent)*. Centrifuge at 2500 rpm for 15 minutes to get a clear supernatant, filter. Dilute 20.0 ml of the filtrate to 100.0 ml with the solvent mixture.

Reference solution (a). A solution of *nilotinib hydrochloride monohydrate IPRS* containing 0.1 per cent w/v of nilotinib in *ethanol (95 per cent)*.

Reference solution (b). Dilute 10.0 ml of reference solution (a) to 50.0 ml with the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 100.0 ml with the solvent mixture.

Reference solution (d). Dilute 1.0 ml of reference solution (c) to 20.0 ml with the solvent mixture.

Reference solution (e). A solution containing 0.002 per cent w/v, each of, *nilotinib impurity D IPRS*, *nilotinib impurity G IPRS* and *nilotinib impurity E IPRS* in *ethanol (95 per cent)*. To 1.0 ml of this solution, add 10 ml of *reference solution (a)* and dilute to 50.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 15 cm × 3.0 mm, packed with end-capped polar embedded octadecylsilane bonded to hybrid silica (3.5 µm) (such as Water Xterra® RP 18),
– column temperature: 40°,
– mobile phase: A. a mixture of 90 volumes of *water*, 10 volumes of *acetonitrile* and 0.25 volumes of *formic acid*,
B. a mixture of 10 volumes of *water*, 90 volumes of *acetonitrile* and 0.1 volumes of *formic acid*,
– a gradient programme using the conditions given below,
– flow rate: 0.8 ml per minute,
– spectrophotometer set at 250 nm,
– injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
6	90	10
16	72	28

25	40	60
26	90	10
30	90	10

Name	Relative retention time	Correction factor
Nilotinib impurity D[1]	0.39	0.9
Nilotinib impurity G[2*]	0.87	---
Nilotinib	1.0	---
Nilotinib impurity F[3*]	1.17	---

*Process impurity included for identification only, not to be calculated and included in total degradation products.
[1]4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzoic acid,
[2] methyl-4-methyl- 3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzoate,
[3]*N*-[3-(4-ethyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide.

Inject reference solution (c) and (e). The test is not valid unless the resolution between the peaks due to nilotinib impurity G and nilotinib is not less than 1.5 in the chromatogram obtained with reference solution (e) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (c),

Inject reference solution (c), (d) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to nilotinib impurity D is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent), the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 0.4 times the area of the principal peak in the chromatogram with reference solution (c) (0.4 per cent). Ignore any peak with an area less than the area of the principal peak in the chromatogram obtained with reference solution (d) (0.05 per cent).

Uniformity of dosage units (2.5.4). Complies with the test stated under Uniformity of dosage units.

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (b) and the test solution.

Calculate the content of $C_{28}H_{22}F_3N_7O$ in the capsules.

1 mg of nilotinib hydrochloride monohydrate, $C_{28}H_{23}F_3N_7O$, HCl, H_2O is equivalent to 0.9066 mg of nilotinib (anhydrous), $C_{28}H_{22}F_3N_7O$.

Labelling. The label states the strength in terms of the equivalent amount of nilotinib.

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