Nilotinib Hydrochloride Monohydrate

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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 arnd-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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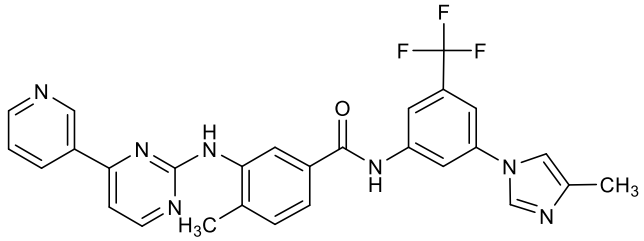
Nilotinib Hydrochloride Monohydrate



, HCl , H_2O

$C_{28}H_{23}ClF_3N_7O,H_2O$ Mol. Wt. 584.0

Nilotinib Hydrochloride Monohydrate is 4-Methyl-*N*-[3-(4-methyl-1*H*-imidazol-l-yl)-5-(trifluoromethyl)phenyl] -3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide hydrochloride monohydrate.

Nilotinib Hydrochloride Monohydrate contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{28}H_{23}ClF_3N_7O$, calculated on the anhydrous basis.

Category. Tyrosine kinase (BCR-ABL) inhibitor.

Description. A white or slightly yellowish or slightly greenish-yellow, hygroscopic, crystalline powder. It shows polymorphism (2.5.11).

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

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *nilotinib hydrochloride monohydrate IPRS* or with the reference spectrum of nilotinib hydrochloride monohydrate.

[NOTE – If the spectrum obtained in the solid state show differences, dissolve the substance under examination and references substance separately in ethanol, evaporate to dryness and record new spectrum using residues]

B. It gives reaction (B) of chlorides (2.3.1).

Tests

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. Dissolve 0.3 g of the substance under examination in 2 ml of *dimethyl sulphoxide* and 7 ml of water, allow to equilibrate at room temperature without shaking to avoid foam formation, and dilute to 10.0 ml with *water*. Shake well, allow the substance under examination to precipitate for about 2 hours in the dark and filter the supernatant liquid through 0.45 µm filter.

Reference solution (a). A 0.0075 per cent w/v solution of *nilotinib impurity A IPRS* in *dimethyl sulphoxide*. Dilute 1.0 ml of the solution to 100.0 ml with *dimethyl sulphoxide*. Dilute 2.0 ml of the solution to 10.0 ml with *water.*

Reference solution (b). A solution containing 0.0075 per cent w/v, each of, *nilotinib impurity B IPRS* and *nilotinib impurity C IPRS* in *dimethyl sulphoxide*. Dilute 1.0 ml of the solution to 100.0 ml with *dimethyl sulphoxide*. Dilute 2.0 ml of the solution to 10.0 ml with *water*.

Reference solution (c). Dilute 2.0 ml of reference solution (b) to 10.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm × 3 mm, packed with polar-embedded octadecylsilane bonded to porous 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
2	85	15
10	80	20
12	75	25
18	10	90
19	10	90
20	85	15
25	85	15

Name	Relative retention time
Nilotinib impurity A[1]	0.3
Nilotinib (Retention time: about 17 minutes)	1.0

[1]3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)aniline.

Inject reference solution (a) to identify the peaks due to nilotinib impurity A.

Inject reference solution (a). The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of peak corresponding to nilotinib impurity A is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3 ppm).

Nilotinib impurities B and C. Determine by liquid chromatography (2.4.14). as described under Nilotinib impurity A with the following modifications.

Chromatographic system
– spectrophotometer set at 225 nm,

Name	Relative retention time
Nilotinib impurity C[2]	0.2
Nilotinib impurity B[3]	0.6
Nilotinib (Retention time: about 17 minutes)	1.0

[2]3-amino-4-methylbenzoic acid,
[3]methyl 3-amino-4-methylbenzoate.

Inject reference solution (b) and (c). The test is not valid unless the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b), for both peaks and the signal-to-noise ratio is not less than 10 for both peaks in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to nilotinib impurity B and nilotinib impurity C, each of, is not more than 0.4 times the area of the principal peaks in the chromatogram obtained with reference solution (b) (2 ppm).

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light.

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

Test solution. Dissolve 20 mg of the substance under examination in the solvent mixture and dilute to 200.0 ml with the solvent mixture.

Reference solution (a). A 0.01 per cent w/v solution of *nilotinib hydrochloride monohydrate IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the *solvent mixture*. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). Dissolve 2 mg of *nilotinib for system suitability IPRS* (containing nilotinib impurities E, F and G) in the solvent mixture and dilute to 20.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm × 3 mm, packed with end-capped octadecylsilane bonded to porous silica (3 µm) (such as YMC-Pack ODS AQ-HP) *[NOTE – Column is compatible with 100 per cent aqueous mobile phase]*,
- 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: 0.8 ml per minute,
- spectrophotometer set at 240 nm,
- injection volume: 5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
2	90	10
16	10	90
17	10	90
18	90	10
25	90	10

Name	Relative retention time
Nilotinib (retention time: about 12 minutes)	1.0
Nilotinib impurity E[1]	1.03
Nilotinib impurity F[2]	1.07
Nilotinib impurity G[3]	1.09

[1]*N*-[3-(1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide,
[2]*N*-[3-(4-ethyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzamide,
[3]methyl-4-methyl- 3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]benzoate.

Inject reference solution (c) to identify the peaks due to nilotinib impurities E, F and G.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to nilotinib impurity F and nilotinib impurity G is not less than 1.5 and the peak-to-valley ratio (Hp/Hv) is not less than 2.0, where Hp is the height above the baseline of the peak due to nilotinib impurity E and Hv is the height above the baseline of the lowest point of the curve separating this peak due to nilotinib.

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to nilotinib impurity F is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than 4 times the area of the principal peak in the chromatogram with reference solution (b) (0.4 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Sulphated ash (2.3.18). Not more than 0.1 per cent, determined on 1 g on a platinum crucible.

Water (2.3.43). 3.0 per cent to 5.0 per cent, determined on 0.15 g, using Hydranal as solvent.

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

Inject reference solution (a) and the test solution.

Calculate the content of $C_{28}H_{23}ClF_3N_7O$.

Storage. Store protected from moisture.

Nilotinib Hydrochloride Monohydrate

Solubility: Slightly soluble in *ethanol*; very slightly soluble in *heptane*; practically insoluble in *water*.