Cabozantinib Tablets

Published on: 19 December, 2022 **Last date for comments:** 27 January, 2023

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 Addendum 2024
Tentative effective date of monograph	July, 2024
First draft published on IPC website for public comments	18 October, 2022
Draft revision published on IPC website for public comments	19 December 2022 (Version 2.0)
Further follow-up action as required.	

Cabozantinib Tablets

Cabozantinib-S-Malate Tablets

Cabozantinib Tablets contain cabozantinib-s-malate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of cabozantinib, $C_{28}H_{24}FN_3O_5$.

Usual strengths. 20 mg; 40 mg; 60 mg.

CAUTION - Cabozantinib 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 the reference solution.

Tests

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 900 ml of *0.01M hydrochloric acid,* with 0.375 per cent w/v of *octoxinol 10* (such as Triton X-100),
Speed and time. 75 rpm and 15 minutes.

Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtrate, suitably diluted with the dissolution medium if necessary, at the maximum at about 333 nm (2.4.7). Calculate the content of $C_{28}H_{24}FN_3O_5$ in the medium from the absorbance obtained from a solution of known concentration of *cabozantinib-s-malate IPRS.*

Q. Not less than 80 per cent of the stated amount of $C_{28}H_{24}FN_3O_5$.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 50 volumes of *acetonitrile,* 50 volumes of *water* and 0.1 volume of *trifluoroacetic acid.*

Test solution. Disperse a quantity of the intact tablets containing 0.2 g of Cabozantinib in the solvent mixture, with the aid of ultrasound for 20 minutes with intermittent shaking and dilute to 200.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 10.0 ml with the solvent mixture and filter.

Reference solution (a). A 0.0634 per cent w/v solution of *cabozantinib-s-malate IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

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

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous (5 µm) (Such as ACE C 18),
- sample temperature: 10°,
- mobile phase: A. 0.1 per cent v/v solution of *orthophosphoric acid* in *water*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1.5 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	80	20
5	75	25
15	75	25
30	62	38
40	45	55
45	22	78
50	22	78
52	80	20
60	80	20

Name	Relative retention time
Cabozantinib impurity A[1]*	0.38
Open ring hydroxy cabozantinib[2]	0.71
Malic acid adduct of cabozantinib[3]	0.77
Cabozantinib	1.0
Dimer of cabozantinib[4]	1.21

*Process impurity included for identification only, this impurity is monitored in the drug substances and not included in the calculation of total degradation products.
[1]1-({4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl} carbamoyl)cyclopropanecarboxylic acid.
[2]N-(4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl)-N'-(4-fluorophenyl)-2-(2-hydroxyethyl)propanediamide.
[3]4-(4-((4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl)amino)-3-[(4-fluorophenyl)carbamoyl]-4-oxobutoxy)-3-hydroxy-4-oxobutanoic acid.
[4]1-(4-((4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl)amino)-3-[(4-fluorophenyl)carbamoyl]-4-oxobutyl)-4-(4-[((1-[(4fluorophenyl)carbamoyl]Cyclopropyl)carbonyl) amino]phenoxy)-6,7-dimethoxyquinolinium.

Inject reference solution (a) and (b). The test is not valid unless the tailing factor is not more than 1.5, 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 (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to open ring hydroxy cabozantinib and dimer of cabozantinib, each of, is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any peak corresponding to malic acid adduct of cabozantinib is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent) and the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (2.0 per cent). Ignore any peak with an area less than 0.01 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Other tests. Comply with the tests stated under Tablets.

Assay. Determine by liquid chromatography (2.4.14).

Solvent mixture. 50 volumes of *acetonitrile*, 50 volumes of *water* and 0.1 volume of *trifluoroacetic acid.*

Test solution. Disperse a suitable quantity of the intact tablets containing 0.2 g of Cabozantinib in the solvent mixture, with the aid of ultrasound for 20 minutes with intermittent shaking and dilute to 250.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 20.0 ml with the solvent mixture and filter.

Reference solution. A 0.00507 per cent w/v solution of *cabozantinib-s-malate IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous (5 µm) (Such as ACE C 18),
- sample temperature: 10°,
- mobile phase: a mixture of 60 volumes of a mixture containing 0.2 per cent v/v solution of *orthophosphoric acid* and 0.2 per cent v/v *triethylamine* in *water* and 40 volumes of *acetonitrile*,
- flow rate: 1.8 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 10 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{28}H_{24}FN_3O_5$ in the tablets.

1 mg of cabozantinib-s-malate is equivalent to 0.789 mg of cabozantinib.

Storage. Store at a temperature not exceeding 30°.

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