Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

Cabozantinib-S-Malate

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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
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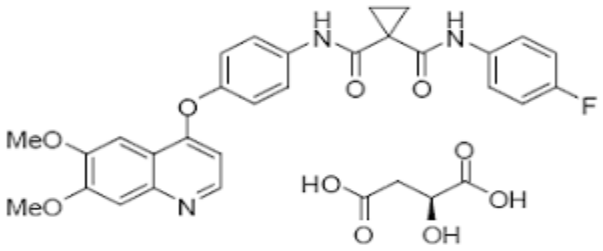
Further follow-up action as required.	

Cabozantinib-S-Malate



$C_{32}H_{30}FN_3O_{10}$ Mol. Wt. 635.6

Cabozantinib-S-Malate is N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate.

Cabozantinib-S-Malate contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{32}H_{30}FN_3O_{10}$, calculated on the anhydrous basis.

CAUTION - Cabozantinib is cytotoxic; extra care required to prevent inhaling particles and exposing the skin to it.

Category. Anticancer

Description. A off white to pale yellow powder, slightly hygroscopic.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *cabozantinib*-s-*malate IPRS* or with the reference spectrum of cabozantinib-s-malate.

B. 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

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. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 5 minutes and dilute to 100.0 ml with the solvent mixture.

Reference solution (a). A 0.0025 per cent w/v solution of *cabozantinib-s-malate IPRS* in the solvent mixture. Dilute 3.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.5 per cent w/v of *cabozantinib-s-malate IPRS* and 0.00075 per cent w/v of *cabozantinib impurity A IPRS (ethyl 1-({4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}carbamoyl) cyclopropanecarboxylate* in the solvent mixture. Dilute 1.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). Dilute 3.0 ml of reference solution (a) to 10.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous (1.8 µm) (Such as Acquity HSS C18),
- 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: 0.5 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 1 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0.0	90	10
5.0	65	35
7.0	65	35
8.5	50	50
11.5	30	70
13.0	30	70
13.1	90	10
17.0	90	10

Name	Relative retention time	Correction factor
Cabozantinib impurity A[1]	0.66	0.72
Cabozantinib	1.0	-

[1]1-({4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl} carbamoyl)cyclopropanecarboxylic acid

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to cabozantinib impurity A and cabozantinib is not less than 1.1 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 for the principal peak in the chromatogram obtained with reference solution (c).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to cabozantinib impurity A is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 per cent), the area of any other secondary peak is not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent), and the sum of the areas of all the secondary peaks is not more than 6.7 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.067 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.01 per cent).

Heavy metals (2.3.13). 2.0 g complies with the limit test for heavy metals, Method B (10 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent, using platinum crucible.

Water (2.3.43). Not more than 5.0 per cent, determined on 0.25 g.

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. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 5 minutes with intermittent shaking and dilute 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. A 0.005 per cent w/v solution of *cabozantinib-s-malate IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 10 cm x 2.1 mm, packed with octadecylsilane bonded to porous (1.8 µm) (Such as Acquity HSS C18),
- sample temperature: 10°,
- mobile phase: a mixture of 62 volumes of a mixture containing 0.2 per cent v/v solution of *orthophosphoric acid* and 0.2 per cent v/v of *triethylamine* in *water*, and 38 volumes of *acetonitrile,*
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 1 µl.

Inject the reference solution. The test is not valid unless, the tailing factor is not more than 1.8 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{32}H_{30}FN_3O_{10}$.

Storage. Store at a temperature between 2° to 8°.

Solubility (2.4.26). Freely soluble in *dimethyl sulphoxide*, very slightly soluble in *methanol* and practically insoluble in *water*.