Sunitinib Malate

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

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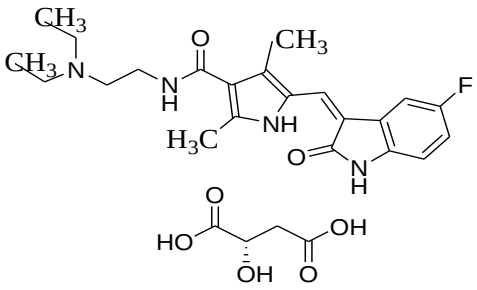
Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls 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	01.08.2024
Draft revision published on IPC website for public comments	08.10.2024
Further follow-up action as required.	

Sunitinib Malate



$C_{22}H_{27}FN_4O_2$. $C_4H_6O_5$ Mol. Wt. 532.6

Sunitinib Malate is (Z)-N-[2-(Diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide(S)-2-hydroxysuccinate.

Sunitinib Malate contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{22}H_{27}FN_4O_2$. $C_4H_6O_5$, calculated on the anhydrous basis.

Category. Antineoplatic agent.

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

Description. A light yellow to brownish orange powder.

Identification

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

~~***L*-Ascorbic Acid.** Not more than 0.1 per cent.~~

~~*Solvent mixture*. 35 volumes of *acetonitrile* and 65 volumes of *water*.~~

~~*Test solution*. Dissolve 25 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 2 minutes and dilute to 50.0 ml with the solvent mixture.~~

~~*Reference solution (a)*. A 0.0075 per cent w/v solution of *L-ascorbic acid IPRS* in the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.~~

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

~~Chromatographic system~~
~~— a stainless steel column 25 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (Such as Kromasil C8),~~
~~— sample temperature: 10°,~~
~~— column temperature: 30°,~~
~~— mobile phase: A. a buffer solution prepared by dissolving 0.77 g of *ammonium acetate* in 1000 ml of *water*,~~
~~B. *acetonitrile*,~~
~~— a gradient programme using the conditions given below,~~
~~— spectrophotometer set at 267 nm,~~
~~— injection volume: 10 µl.~~

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)	Flow rate (ml per min.)
0	96	4	0.5
10	96	4	0.5
12	20	80	1.0
20	20	80	1.0
22	96	4	0.5
35	96	4	0.5

Inject reference solution (a) and (b). The test is not valid unless the column efficiency is not less than 7000 theoretical plates, the tailing factor is not more than 1.5, the relative standard deviation of 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 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution.

Calculate the content of L-ascorbic acid.

Malic acid. Not less than 24.2 per cent and not more than 26.2 per cent, calculated on the anhydrous basis.

Weigh and transfer 0.2 g of the substance under examination to a 150-ml beaker, add dissolved in 100 ml of water and sonicate to dissolve with intermittent shaking. Titrate with *0.1 M sodium hydroxide* determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.1 M sodium hydroxide* is equivalent to 0.006705 g of $C_4H_6O_5$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Protect the solutions from light.

Solvent mixture. 35 volumes of *acetonitrile* and 65 volumes of *water*.

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 2 minutes and dilute to 25.0 ml with the solvent mixture.

Reference solution (a). A 0.0003 per cent w/v solution of *sunitinib malate IPRS* in the solvent mixture.

Reference solution (b). A solution containing 0.0004 per cent w/v, each of, *desethyl sunitinib IPRS* and *sunitinib N-oxide IPRS* and 0.2 per cent w/v of *sunitinib malate IPRS* in 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 25 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (Such as Kromasil C8),
- column temperature: 35°,
- sample temperature: 10°,
- mobile phase: A. a mixture of 90 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, add 1.0 ml of *triethylamine*, adjusted to pH 6.5 with *dilute orthophosphoric acid* and 10 volumes of mobile phase B,

  B. a mixture of equal volumes 50 volumes of *acetonitrile* and 50 volumes of *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 235 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	87	13
5	87	13

40	50	50
45	50	50
55	30	70
60	30	70
62	87	13
70	87	13

Name	Relative retention time	Correction factor
Malic acid	0.07	---
~~L-ascorbic acid~~	~~0.08~~	
Trans isomer of sunitinib[1]	0.63	0.91
Desethyl sunitinib[2]	0.82	0.94
Sunitinib-N-oxide[3]	0.87	0.97
~~Hydroxy impurity of sunitinib[4]~~	~~0.90~~	~~0.72~~
~~Formyl impurity of sunitinib[5]~~	~~0.96~~	~~0.84~~
Sunitinib (Retention time: about 40 minutes)	1.0	---
Desdiethyl amino sunitinib[~~4~~6]	1.12	0.72

[1](E)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide.
[2](Z)-N-[2-(ethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide.
[3](Z)-N-[2-(diethyl-N-oxoamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide.
~~[4](Z)-N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2-(hydroxymethyl)-4-methyl-1H-pyrrole-3-carboxamide.~~
~~[5](Z)-N-[2-(diethylamino)ethyl]-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2-formyl-4-methyl-1H-pyrrole-3-carboxamide.~~
~~[4~~6](Z)-N-ethyl-5-[(5-fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to to desethyl sunitinib and sunitinib-N-oxide is not less than 3.5 in the chromatogram obtained with reference solution (b), the column efficiency is not less than 84000 theoretical plates, the tailing factor is not more than 1.5, the relative standard deviation of 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 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 trans isomer of sunitinib, desethyl sunitinib, sunitinib N-oxide ~~hydroxy impurity of sunitinib, formyl impurity of sunitinib~~ and desdiethyl amino sunitinib, each of, 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 0.67 times 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 6.67 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore the peak due to malic acid~~, L-ascorbic acid~~.

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). Not more than ~~5.0~~ 0.75 per cent, determined on 0.5 g.

Assay. Determine by liquid chromatography (2.4.14),

NOTE — Protect the solutions from light.

Solvent mixture. 35 volumes of *acetonitrile* and 65 volumes of *water*.

Test solution. Dissolve 100 mg of the substance under examination in the solvent mixture with the aid of ultrasound for 2 minutes and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution. A 0.01 per cent w/v solution of *sunitinib malate IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm × 4.6 mm, packed with octylsilane bonded to porous silica (5 µm) (Such as Kromasil C8),
- column temperature: 30°,

- mobile phase: a mixture of 70 volumes of a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water*, add 1.0 ml of *triethylamine*, adjusted to pH 6.5 with *dilute orthophosphoric acid* and 30 volumes *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 15 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2500 theoretical plates, the tailing factor is not more than 1.7 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 $C_{22}H_{27}FN_4O_2$. $C_4H_6O_5$.

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

Solubility.

Sunitinib Malate: Soluble in *dimethylsulphoxide*, slightly soluble in *water* and practically insoluble in *n-heptane*.