Lenvatinib Capsules

Lenvatinib Mesylate Capsules

Lenvatinib Capsules contain lenvatinib mesylate equivalent to not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of lenvatinib, $C_{21}H_{19}ClN_4O_4$.

Usual strengths. 4 mg; 10 mg.

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.

CAUTION –Lenvatinib mesylate is cytotoxic, extra care required to prevent inhaling particles and exposing the skin to it.

Tests

Dissolution (2.5.2).
Apparatus No. 2 (paddle),
Medium.900 ml of *0.1M hydrochloric acid,*
Speed and time. 50 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Use the filtrate, dilute if necessary with the dissolution medium.

Reference solution. Dissolve 45 mg of *lenvatinib mesylate IPRS* in 10 ml of *methanol,* with the aid of ultrasound for 5 minutes and dilute to 100.0 ml with the dissolution medium. Dilute a suitable volume of the solution with the dissolution medium to obtained a solution having known concentration to the expected concentration of the test solution.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40º,
- sample temperature: 10°,
- 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 ml of *triethylamine,* adjusted to pH 3.8 with *dilute orthophosphoric acid* and 30 volumes of *acetonitrile,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 245 nm,
- injection volume: 25 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 4000 theoretical plates, 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 $C_{21}H_{19}ClN_4O_4$in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{21}H_{19}ClN_4O_4$.

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture (a). Equal volumes of *methanol* and *water.*

Solvent mixture (b). 70 volumes of *methanol* and 30 volumes of *water.*

Test solution. Disperse a suitable quantity of intact capsules containing 20 mg of lenvatinib in 60 ml of solvent mixture (b), with the aid of ultrasound for about 30 minutes with intermittent shaking, dilute to 100.0 ml with solvent mixture (b), mix and filter.

Reference solution (a). Dissolve 30.6 mg of *lenvatinib mesylate IPRS* in 40 ml of *methanol* and dilute to 100.0 ml with solvent mixture (a). Dilute 5.0 ml of the solution to 50.0 ml with solvent mixture (b). Further dilute 4.0 ml of the solution to 50.0 ml with solvent mixture (b).

Reference solution (b). Dilute 4.0 ml of reference solution (a) to 100.0 ml with solvent mixture (b).

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Xbridge Shield RP18),
- sample temperature: 10°,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water* adjusted to pH 3.25 with *dilute orthophosphoric acid*,
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 250 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	90	10
15	70	30
20	70	30
35	60	40
45	60	40
55	30	70
57	90	10
65	90	10

Name	Relative retention time	Correction factor
Descyclopropyl lenvatinib[1]	0.66	0.93
Methyl analogue of lenvatinib[2*]	0.78	-
Lenvatinib carboxylic acid[3]	0.83	1.19
Carbamate derivative of APQC[4*]	1.90	-
Lenvatinib	1.00	-
Carbamoyl derivative of lenvatinib[5*]	2.17	-
Nitrile analogue of lenvatinib[6]	2.49	1.13

* Process impurity included for identification only and not included in the calculation of total degradation products.
[1]4-[4-(carbamoylamino)-3- chlorophenoxy]-7- methoxyquinoline-6- carboxamide
[2]4-(3-chloro-4- [(methylcarbamoyl)amino]phenoxy)-7-methoxyquinoline-6-carboxamide
[3]4-(3-chloro-4- [(cyclopropylcarbamoyl)ami no]phenoxy)-7- methoxyquinoline-6- carboxylic acid
[4]phenyl (4-[(6-carbamoyl-7- methoxyquinolin-4-yl)oxy]- 2-chlorophenyl)carbamate
[5]4-(3-chloro-4- [(cyclopropylcarbamoyl)ami no]phenoxy)-N- (cyclopropylcarbamoyl)-7- methoxyquinoline-6- carboxamide
[6]1-(2-chloro-4-[(6-cyano-7- methoxyquinolin-4- yl)oxy]phenyl)-3- cyclopropylurea

Inject reference solution (a) and (b). The test is not valid unless the column efficiency is not less than 50000 theoretical plates, the tailing factor is not more than 1.5 and relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a), 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 descyclopropyl lenvatinib, lenvatinib carboxylic acid and nitrile analogue of lenvatinib, 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 other secondary peak is not more than 0.2 times of the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Uniformity of Content. Complies with the test stated under Capsules.

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

Test solution. Disperse one capsule in 25 ml of solvent mixture (a), with the aid of magnetic stirrer for 20 minutes, add 15 ml of solvent mixture (b), sonicate for 10 minutes and dilute to 50.0 ml with solvent mixture (b). Dilute a suitable volume of the solution with solvent mixture (c) to obtain a solution containing 0.004 per cent w/v of lenvatinib.

Inject the reference solution and the test solution.

Calculate the content of the $C_{21}H_{19}ClN_4O_4$ in the capsule.

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14).
Solvent mixture (a). 90 volumes of *methanol* and 10 volumes of *water.*
Solvent mixture (b). 50 volumes of *methanol* and 50 volumes of *water.*
Solvent mixture (c). 70 volumes of *methanol* and 30 volumes of *water.*

Test solution. Disperse a suitable quantity of intact capsules containing 40 mg of the lenvatinib in 100 ml of solvent mixture (a), with the aid of magnetic stirrer for 20 minutes. Add 50 ml of solvent mixture (b), sonicate for 10 minutes with intermittent shaking and dilute to 200.0 ml with solvent mixture (b). Dilute 2.0 ml of the solution to 10.0 ml with solvent mixture (c).

Reference solution. Dissolve 50 mg of *lenvatinib mesylate IPRS* in 40 ml of *methanol* and dilute to 100.0 ml with solvent mixture (b). Dilute 1.0 ml of the solution to 10.0 ml with solvent mixture (c).

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (3.5 µm) (Such as XBridge C 18),
- column temperature: 40º,
- sample temperature: 10°,
- mobile phase: A. a buffer solution prepared by dissolving 1.36 g of *potassium dihydrogen orthophosphate* in 1000 ml of *water,* adjusted to pH 3.35 with *dilute orthophosphoric acid,*
  B. *acetonitrile*,
- a gradient programme using the conditions given below,
- flow rate: 1 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	75	25
8	75	25
10	35	65
15	35	65
17	75	25
25	75	25

Inject the reference solution. The test is not valid unless the column efficiency is not less than 5000 theoretical plates, 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 $C_{21}H_{19}ClN_4O_4$ in the capsules. 1 mg of the lenvatinib mesylate, $C_{21}H_{19}ClN_4O_4.CH_4O_3S$ is equivalent to 0.816 mg of lenvatinib, $C_{21}H_{19}ClN_4O_4$.

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

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