Etravirine Tablets

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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

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Etravirine Tablets

Etravirine Tablets contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of etravirine, $C_{20}H_{15}BrN_6O$.

Usual strengths. 25 mg; 100 mg; 200 mg.

Identification

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

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the principal peak in the chromatogram obtained with reference solution (a).

Tests

Dissolution (2.5.2).

NOTE— Protect the solutions from light.

Apparatus No. 2 (Paddle),
Medium:
For Tablets labeled to contain 25 mg and 100 mg: 900 ml of a buffer solution prepared by mixing 500 ml of *0.01 M hydrochloric acid* and 400 ml of 2.25 per cent w/v solution of *sodium lauryl sulphate* in *0.01 M hydrochloric acid,*
For Tablets labeled to contain 200 mg: 1800 ml of a buffer solution prepared by mixing 1000 ml of *0.01 M hydrochloric acid* and 800 ml of 2.25 per cent w/v solution of *sodium lauryl sulphate* in *0.01 M hydrochloric acid,*
Speed and time:
For Tablets labeled to contain 25 mg and 100 mg: 50 rpm and 45 minutes;
For Tablets labeled to contain 200 mg: 70 rpm and 30 minutes;

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Test solution. Place 1 tablet in each vessel filled with a volume of *0.01 M hydrochloric acid* as specified in medium. After 10 minutes, add a volume of preheated 2.25 per cent w/v of *sodium lauryl sulphate* in *0.01 M hydrochloric acid* as specified in medium and reset the time to zero. Use the filtrate, dilute if necessary, with the dissolution medium.

Reference solution. Transfer a suitable quantity of *etravirine IPRS* to a suitable volumetric flask and dissolve in 5 per cent of the total volume of *1-methyl-2-pyrrolidone,* add *acetonitrile* 50 per cent of the total volume, equilibrate to room temperature and dilute to volume with 2.25 per cent w/v solution of *sodium lauryl sulphate* in *0.01 M hydrochloric acid* to obtain a solution having similar concentration to that of the test solution.

Chromatographic system
- a stainless steel column 5.0 cm x 3.0 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as XTerra MS C18),
- column temperature: 35°,
- mobile phase: a mixture of 65 volumes of *acetonitrile* and 35 volumes of 0.5 per cent v/v of *orthophosphoric acid* in *water*,
- flow rate: 0.5 ml per minute,
- spectrophotometer set at 260 nm,
- injection volume:
For Tablets labeled to contain 25 mg: 40 µl,
For Tablets labeled to contain 100 mg and 200 mg: 10 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 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 $C_{20}H_{15}BrN_6O$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_{20}H_{15}BrN_6O$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE— Protect the solutions from light.

Buffer solution. A *0.01M ammonium formate* in *water.*

Solvent mixture. Equal volumes of *acetonitrile* and the buffer solution.

Test solution. Disperse a quantity of the powder containing 50 mg of Etravirine in 25 ml of the solvent mixture with the aid of mechanical shake for 5 minutes. Add 25 ml of *1-methyl-2-pyrrolidone* and shake for 30 minutes, dilute to 500.0 ml with the solvent mixture. Allow the solution to stand for 4 hours at room temperature, filter.

Reference solution (a). Dissolve 25 mg of *etravirine IPRS* in 2.5 ml of *1-methyl-2-pyrrolidone* and dilute to 50.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 25.0 ml with the solvent mixture.

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

Reference solution (c). Transfer a suitable amount of *etravirine system suitability mixture IPRS* to a suitable volumetric flask and dissolve in 10 per cent of the total volume of *1-methyl-2-pyrrolidone*, dilute to volume with the solvent mixture.

Reference solution (d). Dilute 5.0 ml of reference solution (b) to 100.0 ml in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 3.0 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as YMC- Pack Pro C18 RS),
- column temperature: 35°,
- mobile phase: A. a *0.05M formic acid* in the buffer solution,
  B. *acetonitrile,*
  C. *methanol,*
- a gradient programme using the conditions given below,
- flow rate: 0.6 ml per minute,
- spectrophotometer set at 310 nm,
- injection volume: 10 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)	Mobile phase C (per cent v/v)
0	60	30	10
35	0	0	100
37	60	30	10
45	60	30	10

Name	Relative retention time
Etravirine amino analog[1]	0.66
Desbromoetravirine [2]	0.73
Etravirine	1.0

[1]4-[(4-Amino-5-bromo-6-chloropyrimidin-2-yl)amino]benzonitrile.
[2] 4-{[6-Amino-2-{(4-cyanophenyl)amino}pyrimidin-4-yl]oxy}-3,5-dimethylbenzonitrile.

Inject reference solution (a), (c) and (d). The test is not valid unless the resolution between the peaks due to etravirine amino analog and desbromoetravirine is not less than 4.3 in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10.0 in the chromatogram obtained with reference solution (d).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference

solution (b) (0.2 per cent) and the sum of the areas of all the secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

Uniformity of dosage units (2.5.4). Comply with the tests stated under Tablets.

Other tests. Comply with the tests stated under Tablets.

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

Inject reference solution (a). 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 1.0 per cent.

Inject reference solution (a) and the test solution.

Calculate the content of $C_{20}H_{15}BrN_6O$ in the tablets.

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