Etravirine

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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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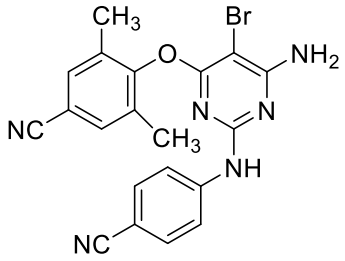
Etravirine



$C_{20}H_{15}BrN_6O$ Mol. Wt. 435.3

Etravirine is Benzonitrile, 4-[[6-amino-5-bromo-2-[(4-cyanophenyl) amino]-4-pyrimidinyl]oxy]-3,5-dimethyl.

Etravirine contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{20}H_{15}BrN_6O$, calculated on the anhydrous and solvent-free basis.

Category. Anti-retroviral.

Description. A white to off-white powder.

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

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. 50 volumes of *acetonitrile* and 45 volumes of buffer solution.

Test solution. Dissolve 50 mg of the substances under examination in *1-methyl-2-pyrrolidone* and dilute to 25.0 ml with *1-methyl-2-pyrrolidone*. Dilute 1.0 ml of the solution to 20.0 ml with the solvent mixture.

Reference solution (a). A 0.2 per cent w/v solution of *etravirine IPRS* in *1-methyl-2-pyrrolidone*. Dilute 1.0 ml of the solution to 20.0 ml with the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml in 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* and dilute to volume with the solvent mixture.

Reference solution (d). Dilute 5.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 100.0 ml with the 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	Correction factor
Etravirine amino analog[1]	0.66	0.77
Desbromoetravirine [2]	0.73	---
Etravirine	1.0	---
Etravirine butanamide analog[3]	1.08	1.30
Etravirine dimer [4]	1.41	1.16

[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.
[3]4-{[5-Bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]pyrimidin-4-yl](methyl)amino}butanamide.
[4]4,4'-{[5-Bromo-2-[(4-cyanophenyl)amino]pyrimidine-4,6-diyl]bis(oxy)}bis(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), the relative standard deviation for replicate injections is not more than 1.0 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 (d).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to etravirine amino analog and desbromoetravirine, each of, is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent), the area of any peak corresponding to etravirine butanamide analog is not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent), the area of any peak corresponding to etravirine dimer is not more than 0.5 time the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent) and the sum of the areas of all the secondary peaks is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent). Ignore any peak with an area less than 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.3.43). Not more than 0.5 per cent.

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 $C_{20}H_{15}BrN_6O$.

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