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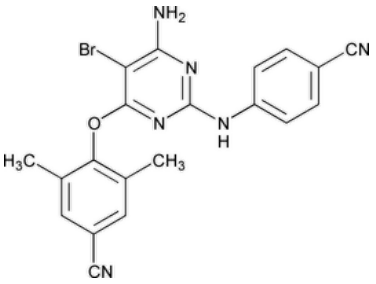
Add the following:

▲Etravirine



$C_{20}H_{15}BrN_6O$ 435.29

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

4-({6-Amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl}oxy)-3,5-dimethyl-benzonitrile CAS RN®: 269055-15-4; UNII: 0C50HW4FO1.

DEFINITION

Etravirine contains NLT 98.0% and NMT 102.0% of etravirine ($C_{20}H_{15}BrN_6O$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K or 197A

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Protect solutions containing etravirine from light.

Buffer: 10 mM ammonium formate in water

Diluent: Acetonitrile and *Buffer* (10:9, v/v)

Solution A: 50 mM formic acid in *Buffer*

Solution B: Acetonitrile

Solution C: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	60	30	10
35	0	0	100
37	60	30	10
45	60	30	10

Standard stock solution: 2.0 mg/mL of USP Etravirine RS in 1-methyl-2-pyrrolidone

Standard solution: 0.10 mg/mL of USP Etravirine RS from the *Standard stock solution* in *Diluent*

Sample stock solution: 2.0 mg/mL of Etravirine in 1-methyl-2-pyrrolidone

Sample solution: 0.10 mg/mL of Etravirine from the *Sample stock solution* in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 310 nm

Column: 3.0-mm × 15-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 0.6 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of etravirine ($C_{20}H_{15}BrN_6O$) in the portion of Etravirine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of etravirine from the *Sample solution*

r_S = peak response of etravirine from the *Standard solution*

C_S = concentration of USP Etravirine RS in the *Standard solution* (mg/mL)

C_U = concentration of Etravirine in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0%, on the anhydrous and solvent-free basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities**

Protect solutions containing etravirine from light.

Buffer, Diluent, Solution A, Solution B, Solution C, Mobile phase, Standard stock solution, Standard solution, Sample stock solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 0.10 mg/mL of USP Etravirine System Suitability Mixture RS prepared as follows. Transfer a suitable amount of USP Etravirine System Suitability Mixture RS to a suitable volumetric flask and dissolve in 10% of the total volume of 1-methyl-2-pyrrolidone. Dilute with *Diluent* to volume.

Sensitivity solution: 0.05 µg/mL of USP Etravirine RS from the *Standard solution* in *Diluent*

System suitability

Samples: *Standard solution*, *System suitability solution*, and *Sensitivity solution*

[Note—The relative retention times for etravirine amino analog and desbromoetravirine in relation to etravirine are 0.66 and 0.73, respectively.]

Suitability requirements

Resolution: NLT 4.3 between etravirine amino analog and desbromoetravirine, *System suitability solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Etravirine taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of any individual impurity from the *Sample solution*

r_S = peak response of etravirine from the *Standard solution*

C_S = concentration of USP Etravirine RS in the *Standard solution* (mg/mL)

C_U = concentration of Etravirine in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Etravirine amino analog[a,b]	0.66	1.3	—
Desbromoetravirine[c,b]	0.73	1.0	—
Etravirine	1.0	1.0	—
Etravirine butanamide analog[d]	1.08	0.77	0.30
Etravirine dimer[e]	1.41	0.86	0.50
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] 4-[(4-Amino-5-bromo-6-chloropyrimidin-2-yl)amino]benzonitrile.

[b] For peak identification purpose. If present, these impurities are covered under acceptance criteria for any individual unspecified impurity.

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

[d] 4-{[5-Bromo-6-(4-cyano-2,6-dimethylphenoxy)-2-[(4-cyanophenyl)amino]pyrimidin-4-yl](methyl)amino}butanamide.

[e] 4,4'-{[5-Bromo-2-[(4-cyanophenyl)amino]pyrimidine-4,6-diyl]bis(oxy)}bis(3,5-dimethylbenzonitrile).

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I, Method Ia*:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and store at room temperature.

• **USP Reference Standards ⟨11⟩**

USP Etravirine RS

USP Etravirine System Suitability Mixture RS▲ (USP 1-Dec-2022)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
ETRAVIRINE	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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