

BRIEFING

Efavirenz Tablets. A new USP Pending Monograph is being proposed based on validated methods. The HPLC procedures in the *Assay* and in the test for *Organic Impurities* are based on analyses performed with the Hypersil BDS C18 brand of L1 column. The typical retention time of the efavirenz peak is about 3.3 min for the *Assay* and 10.3 min for the test for *Organic Impurities*.

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C63867

Add the following:

►Efavirenz Tablets

Draft 1

DEFINITION

Efavirenz Tablets contain NLT 92.0% and NMT 110.0% of the labeled amount of efavirenz (C₁₄H₉ClF₃NO₂).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION** (197U)
Wavelength range: 250–300 nm
Medium: Proceed as directed in the test for *Dissolution*.
Sample solution: 16.8 µg/mL of efavirenz in *Medium*
- **B:** The retention time of the efavirenz peak of *Sample solution B* corresponds to that of *Standard solution B*, as obtained in the test for *Organic Impurities*.

ASSAY

- **PROCEDURE**
Buffer: 8.6 mg/mL of ammonium dihydrogen phosphate in water. Adjust with phosphoric acid to a pH of 3.00 ± 0.05. Pass the solution through a suitable 0.45-µm filter.
Mobile phase: Acetonitrile and *Buffer* (3:2)
System suitability solution: 120 µg/mL of USP Efavirenz RS and 1.8 µg/mL of USP Efavirenz Related Compound A RS in methanol
Standard solution: 0.12 mg/mL of USP Efavirenz RS in methanol. Pass the solution through a suitable 0.45-µm filter.
Sample stock solution: Transfer an equivalent to 3000 mg of efavirenz (NLT 5 Tablets) to a 500-mL volumetric flask, add 400 mL of methanol, shake, and sonicate until the Tablets have completely disintegrated. Sonicate for another 20 min with intermittent swirling. Allow the solution to cool to room temperature, and dilute with methanol to volume. Centrifuge an aliquot for 10 min at 500 rpm and use the filtrate.
Sample solution: 0.12 mg/mL of efavirenz from the *Sample stock solution* in methanol. Pass the solution through a suitable 0.45-µm filter.
Chromatographic system
(See *Chromatography* (621), *System Suitability*.)
Mode: LC
Detector: UV 252 nm
Column: 4.6-mm × 15-cm column; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
Column temperature: 30 ± 2°
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times are listed in *Impurity Table 1*.]
Suitability requirements
Resolution: NLT 2 between efavirenz and efavirenz related compound A, *System suitability solution*

Column efficiency: NLT 3000 theoretical plates for efavirenz, *System suitability solution*
Tailing factor: NMT 2.0 for efavirenz, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of C₁₄H₉ClF₃NO₂ in the portion of Tablets taken:

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

- r_U = peak response of efavirenz in the *Sample solution*
- r_S = peak response of efavirenz in the *Standard solution*
- C_S = concentration of USP Efavirenz RS in the *Standard solution* (mg/mL)
- C_U = nominal concentration of efavirenz in the *Sample solution* (mg/mL)

Acceptance criteria: 92.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** (711)
Medium: 2% sodium lauryl sulfate in water; 900 mL, degassed
Apparatus 2: 50 rpm
Time: 30 min
Standard solution: Transfer about 67 mg, accurately weighed, of USP Efavirenz RS to a 200-mL volumetric flask, dissolve in 20 mL of methanol, and dilute with *Medium* to volume. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Medium* to volume.
Sample solution: Pass a portion of the solution under test through a suitable 0.45-µm filter. Transfer 5.0 mL of the filtrate to a 200-mL volumetric flask, and dilute with *Medium* to volume.
Spectrometric conditions
Mode: UV absorption spectroscopy
Analytical wavelength: UV 248 nm
Cell length: 1 cm
Blank: *Medium*
Calculate the percentage of C₁₄H₉ClF₃NO₂ in the portion of Tablets taken:
$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times D \times 100$$

A_U = absorbance of efavirenz from the *Sample solution*
A_S = absorbance of efavirenz from the *Standard solution*
C_S = concentration of USP Efavirenz RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL
D = dilution factor of solution under test
Tolerances: NLT 80% (Q) of the labeled amount of efavirenz is dissolved.
- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

IMPURITIES

Organic Impurities

- **PROCEDURE**
Buffer: Proceed as directed in the *Assay*.
Solution A: Acetonitrile and *Buffer* (1:1)
Solution B: Acetonitrile and *Buffer* (3:1)
Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	100	0
25	0	100
35	0	100
37	100	0
45	100	0

2 / **Efavirenz Tablets**

System suitability solution: 1 mg/mL of USP Efavirenz RS and 2 µg/mL of USP Efavirenz Related Compound A RS in methanol

Standard solution A: 2 µg/mL of USP Efavirenz RS in methanol

Standard solution B: 0.1 mg/mL of USP Efavirenz RS in methanol

Sample solution A: Transfer an equivalent to 200 mg of efavirenz from powdered Tablets (NLT 20) to a 200-mL volumetric flask. Add 150 mL of methanol, and sonicate for 15 min with intermittent swirling to obtain uniform dispersion. Allow the solution to cool to room temperature. Dilute with methanol to volume and pass the solution through a suitable 0.45-µm filter.

Sample solution B: 0.1 mg/mL of efavirenz in methanol from *Sample solution A*

Chromatographic system
(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm column; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection size: 20 µL

System suitability

Sample: *System suitability solution* and *Standard solution A*

Suitability requirements

Resolution: NLT 2.0 between efavirenz and efavirenz related compound A, *System suitability solution*

Column efficiency: NLT 6000 theoretical plates for efavirenz, *System suitability solution*

Tailing factor: NMT 2.0 for efavirenz, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution A*

Analysis

Samples: *Standard solution A* and *Sample solution A*
[NOTE—*Sample solution A* and *Standard solution A* are used for the determination of impurities. *Sample solution B* and *Standard solution B* are used in *Identification test B*.]
Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = response of each impurity peak in *Sample solution A*

r_S = response of efavirenz in *Standard solution A*

C_S = concentration of USP Efavirenz RS in *Standard solution A* (mg/mL)

C_U = nominal concentration of efavirenz in *Sample solution A* (mg/mL)

F = relative response factor for each impurity as listed in *Impurity Table 1*

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Efavirenz related compound A ^a	0.82	0.82	0.2
Efavirenz	1.00	—	—
Efavirenz quinoline analog ^b	2.60	1.1	0.2
Any individual unknown impurity	—	1.0	0.2

^a (S)-2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol.
^b 6-Chloro-2-cyclopropyl-4-(trifluoromethyl)quinoline.

Acceptance criteria

Individual impurities: See *Impurity Table 1*.
Total impurities: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS (11)**
USP Efavirenz RS
USP Efavirenz Related Compound A RS¹ (1-Nov-2009)