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Efavirenz Tablets

DEFINITION
Efavirenz Tablets contain NLT 92.0% and NMT 108.0% of the labeled amount of efavirenz ($C_{14}H_9ClF_3NO_2$).

IDENTIFICATION

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

Sample solution: Completely remove the coating film from a Tablet using a mortar and pestle to crack the Tablet, grind the contents into fine powder, and place the powder into a suitable container. Dissolve the contents in about 5 mL of acetonitrile by mixing on a vortex mixer. Allow to settle, remove about 3 mL of the solution, and centrifuge for about 5 min using a suitable container. Transfer 1–2 mL of supernatant to a clean suitable container, and evaporate to dryness under nitrogen. Mix 0.5–1 mg of the powder with 200 mg of potassium bromide.

Acceptance criteria: Meet the requirements

• **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**

Diluent: Acetonitrile and water (500:500)

Solution A: Methanol, trifluoroacetic acid, and water (100:0.5:900)

Solution B: Methanol, trifluoroacetic acid, and water (900:0.5:100)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
16	50	50
23	35	65
28	30	70
29	20	80
31	20	80
32	60	40
40	60	40

Standard stock solution 1: 0.2 mg/mL of USP Efavirenz Related Compound B RS in *Diluent*

Standard stock solution 2: 5 mg/mL of USP Efavirenz RS in *Diluent*. Sonicate to dissolve before diluting to final volume.

Standard solution: 250 µg/mL of USP Efavirenz RS and 1 µg/mL of USP Efavirenz Related Compound B RS in *Diluent* prepared from *Standard solution stock 2* and *Standard stock solution 1*, respectively. Store protected from light. For the HPLC analysis, it is recommended to use polypropylene vials, because degradation may occur with glass containers.

Sample stock solution: Nominally, 12 mg/mL of efavirenz in *Diluent* prepared as follows. Transfer NLT 10 Tablets to a suitable container, and extract the contents in *Diluent* by mixing for about 90 min. Store protected from light.

Sample solution: Nominally, 240 µg/mL of efavirenz in *Diluent* prepared as follows. Filter a portion of the *Sample stock solution*, and dilute the filtrate with *Diluent*. Store protected from light. For the HPLC analysis, it is recommended to use polypropylene vials, because degradation may occur with glass containers.

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 15-cm; 5-µm packing L10

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 35 µL

System suitability

Sample: *Standard solution*

[NOTE—The typical retention times for efavirenz related compound B and efavirenz are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.2 between efavirenz related compound B and efavirenz

Relative standard deviation: NMT 2.0% for efavirenz

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of efavirenz ($C_{14}H_9ClF_3NO_2$) 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 from the *Sample solution*

r_S = peak response of efavirenz from 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%–108.0%

PERFORMANCE TESTS

• **DISSOLUTION ⟨711⟩**

Medium: 2.0% (w/v) sodium lauryl sulfate in water; 1000 mL. Do not deaerate.

Apparatus 2: 50 rpm, with helix sinker. In addition, paddle and shaft must be composed of stainless steel and not coated with Teflon or other material. Also, all sampling devices and dissolution vessels must be washed with methanol or ethanol followed by a water wash.

Time: 30 min

Standard solution: (*L*/1000) mg/mL of USP Efavirenz RS in *Medium*, where *L* is the Tablet label claim in mg. A small volume of methanol, NMT 1% of the final volume, could be used to solubilize efavirenz. Dilute this solution with *Medium* to obtain a final concentration of about 0.012 mg/mL.

Sample solution: Pass a portion of the solution under test through a suitable polyethylene filter, and dilute with *Medium* to obtain a concentration similar to the *Standard solution*, assuming complete dissolution of the Tablet label claim.

Instrumental conditions

Analytical wavelength: UV 247 nm

Cell: 1 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of efavirenz ($C_{14}H_9ClF_3NO_2$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times V \times D \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

V = volume of *Medium*, 1000 mL

D = dilution for the *Sample solution*

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of efavirenz ($C_{14}H_9ClF_3NO_2$) is dissolved.

Change to read:

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** ▲Meet the requirements▲ (CN 1-Aug-2023)

Procedure for content uniformity

Diluent: Acetonitrile and water (50:50)

Standard solution: 12 µg/mL of USP Efavirenz RS in *Diluent*

Sample solution: Transfer NLT 10 Tablets into separate and suitable containers, and dissolve in 250 mL of *Diluent*. Stir for about 90 min, and centrifuge a portion of each solution for 10 min. Pass about 10 mL through a suitable nylon or PVDF membrane filter. Immediately dilute a portion of the filtrate to an efavirenz concentration of about 12 µg/mL.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: UV 246 nm

Cell: 1 cm

Blank: *Diluent*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of efavirenz ($C_{14}H_9ClF_3NO_2$) in each Tablet 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 the *Sample solution* (mL)

D = dilution factor of the *Sample solution*

▲▲ (CN 1-Aug-2023)

IMPURITIES

• **Organic Impurities**

Diluent, Solution A, Solution B, Sample solution, and **Chromatographic system:** Prepare as directed in the *Assay*.

System suitability solution: Use the *Standard solution* prepared as directed in the *Assay*.

Standard solution: 1.25 µg/mL of USP Efavirenz RS and 0.005 µg/mL of USP Efavirenz Related Compound B RS in *Diluent* from the *System suitability solution*

System suitability

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

Suitability requirements

Resolution: NLT 1.2 between efavirenz related compound B and efavirenz, *System suitability solution*

Relative standard deviation: NMT 5.0% for efavirenz, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual degradation product in the Tablet 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 (degradation product) from the *Sample solution*

r_S = peak response of efavirenz from 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)

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Efavirenz aminoalcohol (degradation product)[a]	0.48	0.26	0.25
Efavirenz ethene analog (efavirenz related compound B)[b,c]	0.93	—	—
Efavirenz	1.0	—	—
Efavirenz pent-3-ene-1-yne (*cis*)[c,d]			
Efavirenz pent-3-ene-1-yne (*trans*)[c,e]		—	—
Efavirenz penteneyne[c,f]	1.16		
Efavirenz pentyne analog[c,g]	1.2	—	—
Methylefavirenz[c,h]	1.28	—	—
Efavirenz aminoalcohol methyl carbamate[c,i]	1.33	—	—
Quinoline analog (degradation product)[i]	1.45	2.0	0.20
Efavirenz aminoalcohol ethyl carbamate[c,k]	1.53	—	—
Unidentified impurity[c]	1.60	—	—
Efavirenz aminoalcohol bis(ethoxycarbonyl)[c,l]	1.63	—	—
N-Benzylefavirenz[c,m]	1.8	—	—
Efavirenz benzoylaminoalcohol[c,n]	1.9	—	—
Unidentified impurity[c]	2.1	—	—
Cyclobutenylindole analog[c,o]	2.18	—	—
Any other individual degradation product	—	1.0	0.20
Total[c,p]	—	—	0.50

[a] (*S*)-2-(2-Amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol.

[b] (*S,E*)-6-Chloro-4-(2-cyclopropylvinyl)-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

[c] For information purposes only. These are process impurities monitored in the drug substance and are not included in the total impurities. Include only the degradation products in the calculation of the total impurities.

[d] (*S,Z*)-6-Chloro-4-(pent-3-en-1-ynyl)-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

[e] (*S,E*)-6-Chloro-4-(pent-3-en-1-ynyl)-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

[f] (*S*)-6-Chloro-4-(3-methylbut-3-en-1-ynyl)-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

[g] (*S*)-6-Chloro-4-(pent-1-ynyl)-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

[h] (*S*)-6-Chloro-4-{[(2*RS*,2*RS*)-2-methylcyclopropyl]ethynyl}-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

[i] (*S*)-Methyl 4-chloro-2-(4-cyclopropyl-1,1,1-trifluoro-2-hydroxybut-3-yn-2-yl)phenylcarbamate.

[j] 6-Chloro-2-cyclopropyl-4-(trifluoromethyl)quinoline.

[k] (*S*)-Ethyl 4-chloro-2-(4-cyclopropyl-1,1,1-trifluoro-2-hydroxybut-3-yn-2-yl)phenylcarbamate.

[l] (*S*)-Ethyl 4-chloro-2-[4-cyclopropyl-2-(ethoxycarbonyloxy)-1,1,1-trifluorobut-3-yn-2-yl]phenylcarbamate.

[m] (*S*)-6-Chloro-4-(cyclopropylethynyl)-1-(4-methoxybenzyl)-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

[n] (*S*)-*N*-[4-Chloro-2-(4-cyclopropyl-1,1,1-trifluoro-2-hydroxybut-3-yn-2-yl)phenyl]-4-methoxybenzamide.

[o] Ethyl 5-chloro-2-cyclobutenyl-3-(trifluoromethyl)-1*H*-indole-1-carboxylate.

[p] Disregard any peak less than 0.05%.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Store in well-closed containers at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Efavirenz RS

USP Efavirenz Related Compound B RS

(*S*,*E*)-6-Chloro-4-(2-cyclopropylvinyl)-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one.

$C_{14}H_{11}ClF_3NO_2$ 317.69

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

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

Chromatographic Database Information: Chromatographic Database

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