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Efavirenz Capsules

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

IDENTIFICATION

Change to read:

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: **197K**▲ (CN 1-May-2020)

Sample solution: Dissolve the contents of 1 Capsule 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. 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.

Change to read:

• **B.** ▲Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: **197U**▲ (CN 1-May-2020)

Solvent: Acetonitrile

Standard solution: 10 µg/mL in *Solvent*

Sample solution: Dissolve the contents of 1 Capsule in about 40 mL of *Solvent* by shaking for about 30 min. Pass through a suitable nylon or PVDF membrane filter, discarding the first 2 mL of filtrate, and dilute a portion with acetonitrile to a concentration of 10 µg/mL of efavirenz.

Acceptance criteria: The UV absorption spectrum of the *Sample solution* exhibits maxima and minima at the same wavelengths as does the *Standard solution*.

ASSAY

• **Procedure**

Diluent: Acetonitrile and water (1:1)

Solution A: Methanol, trifluoroacetic acid, and water (1:0.005:9). [Note—Use only freshly-opened trifluoroacetic acid, ≤6 months.]

Solution B: Methanol, trifluoroacetic acid, and water (9:0.005:1). [Note—Use only freshly-opened trifluoroacetic acid, ≤6 months.]

Mobile phase: See the gradient table below.

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

Standard solution 2: 5 mg/mL of USP Efavirenz RS in acetonitrile. [Note—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 2* and *Standard solution 1*, respectively. [Note—Store protected from light. For the HPLC analysis, it is recommended to use polypropylene vials, because degradation has been noted with certain brands made of glass.]

Sample stock solution: Transfer the contents of NLT 10 Capsules to a suitable container, and extract the contents in acetonitrile by mixing for about 30 min to obtain a quantitative solution equivalent to about 5 mg/mL of efavirenz. [Note—Store protected from light.]

Sample solution: Filter a portion of the *Sample stock solution*, and dilute the filtrate with *Diluent* to obtain a solution of about 250 µg/mL of efavirenz. [Note—Store protected from light. For the HPLC analysis, it is recommended to use polypropylene vials, because degradation has been noted with certain brands made of glass.]

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 15-cm; packing L10

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection size: 35 µL

System suitability

Sample: *Standard solution*

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 efavirenz ($C_{14}H_9ClF_3NO_2$) in the portion of Capsules 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: 1.0% (w/v) sodium lauryl sulfate in water; 900 mL. [Note—Do not deaerate.]

Apparatus 2: 50 rpm, with helix sinker

Time: 45 min

Standard solution: (L/900) mg/mL of USP Efavirenz RS in *Medium*, where L is the Capsule label claim in mg. A small volume of methanol, NMT 10% of the final volume, could be used to solubilize efavirenz. Dilute this solution with *Medium* to obtain a final concentration of about 0.01 mg/mL for Capsules labeled to contain 50 mg, or about 0.02 mg/mL for Capsules labeled to contain 100 mg or 200 mg.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and dilute with *Medium* to obtain a theoretical concentration similar to the *Standard solution*, assuming complete dissolution of the Capsule label claim.

Analytical wavelength: UV 247 nm

Cell: 1 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of efavirenz dissolved:

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Capsule)

D = dilution factor of the *Sample solution*

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of efavirenz is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

Procedure for content uniformity

Standard solution: 10 µg/mL of USP Efavirenz RS in acetonitrile

Sample solution: Transfer the contents of 1 Capsule into a suitable container, and dissolve in 40.0 mL of acetonitrile. Shake for about 30 min and pass through a suitable nylon or PVDF membrane filter. Dilute a portion of the filtrate to an efavirenz concentration of about 10 µg/mL.

Spectrometric conditions

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

Mode: UV absorption spectroscopy

Analytical wavelength: UV 246 nm

Cell: 1 cm

Blank: Acetonitrile

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of efavirenz ($C_{14}H_9ClF_3NO_2$) in the portion of Capsules 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/Capsule)

V = volume of the *Sample solution*

D = dilution factor of the *Sample solution*

IMPURITIES

Organic Impurities

• **Procedure**

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 impurity in the portion of Capsules 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 *Impurity Table 1*)

Acceptance criteria

Individual impurities: See *Impurity Table 1*. [Note—Disregard any peak less than 0.05%.]

Total impurities: NMT 0.50%. [Note—Include only the degradation products in the calculation of the total impurities.]

Impurity Table 1

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

* For information purposes only. These are process impurities monitored in the drug substance and are not included in the total impurities.

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

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

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

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

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

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

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

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

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

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

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

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

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 CAPSULES	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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