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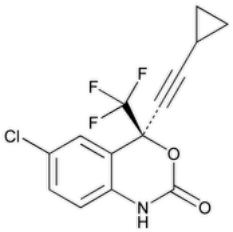
Efavirenz



$C_{14}H_9ClF_3NO_2$ 315.67

1*H*-Benzo[*d*][1,3]oxazin-2(4*H*)-one, 6-chloro-4-cyclopropylethynyl-4-trifluoromethyl;

(*S*)-6-Chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one CAS RN®: 154598-52-4; UNII: JE6H2O27P8.

DEFINITION

Efavirenz contains NLT 98.0% and NMT 102.0% of $C_{14}H_9ClF_3NO_2$, calculated on the anhydrous, solvent-free basis.

IDENTIFICATION

Change to read:

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

Sample: Dry at 105° for 30 min, and cool in dessicator.

Change to read:

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

Solvent: Methanol

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

Sample solution: 10 µg/mL of Efavirenz in *Solvent*

Acceptance criteria: Meets the requirements

ASSAY

• **Procedure**

[Note—Protect solutions of efavirenz from light. Use of polypropylene HPLC vials is recomended to avoid possible degradation from certain types of glass vials.]

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

Time (min)	Solution A (%)	Solution B (%)
40	60	40

Standard solution: 250 µg/mL of USP Efavirenz RS and 1.0 µg/mL of USP Efavirenz Related Compound B RS in *Diluent*. [NOTE—Dissolve in about 65% of the flask volume in *Diluent* and shake for 30 min or until dissolved before diluting with *Diluent* to volume.]

Sample solution: 250 µg/mL of Efavirenz in *Diluent*. [NOTE—Dissolve in about 65% of the flask volume of *Diluent*, and shake for 30 min or until dissolved before diluting with *Diluent* to volume.]

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 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 1.0% for efavirenz

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{14}H_9ClF_3NO_2$ in the portion of Efavirenz taken:

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

r_U = peak response for efavirenz from the *Sample solution*

r_S = peak response for efavirenz from the *Standard solution*

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

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

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

IMPURITIES

Inorganic Impurities

- **Residue on Ignition ⟨281⟩:** NMT 0.2%, use a platinum crucible

Organic Impurities

- **Procedure 1**

Diluent, Solution A, Solution B, Sample solution, and **Chromatographic system:** Proceed 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 in *Diluent*, prepared 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 Efavirenz taken:

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

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

r_S = peak response for efavirenz from the *Standard solution*

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

C_U = 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 1.0%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Efavirenz aminoalcohol[a]	0.48	0.26	0.15
Efavirenz ethene analog[b] (efavirenz related compound B)	0.93	0.91	0.40
Efavirenz pent-3-ene-1-yne (*trans*)[c]	1.16	1.0	0.10[g]
Efavirenz pent-3-ene-1-yne (*cis*)[d]	1.16	1.0	0.10[g]
Efavirenz penteneyne[e]	1.16	1.0	0.10[g]
Efavirenz pentyne analog[f]	1.2	1.0	0.15
Methyl efavirenz[g]	1.28	1.0	0.10
Efavirenz amino alcohol methyl carbamate[h]	1.33	0.83	0.10
N-Benzylefavirenz[i]	1.8	0.71	0.25
Efavirenz benzoylaminoalcohol[j]	1.9	0.56	0.15
Quinoline analog[k]	1.45	2.0	0.10
Efavirenz amino alcohol ethyl carbamate[l]	1.53	0.83	0.10
Unidentified impurity[m]	1.60	1.0	0.10
Efavirenz amino alcohol bis(ethoxycarbonyl)[n]	1.63	0.34	0.10
Unidentified impurity[o]	2.1	1.0	0.10
Cyclobutenylindole analog[p]	2.18	0.48	0.10
Any other unknown individual impurity	—	1.0	0.10

[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-(trifluoromethyl)-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] Relative retention time of 1.60.

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

[o] Relative retention time of 2.1.

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

[q] [NOTE—If results exceed 0.10%, perform *Procedure 2* to separate the three coeluting impurities and ensure that each impurity meets the limit.]

• **PROCEDURE 2**

[NOTE—Perform *Procedure 2* in addition to *Procedure 1* if the result for the total of the three impurities at a relative retention time of 1.16 in *Procedure 1* exceeds 0.10%.]

Diluent: Acetonitrile, trifluoroacetic acid, and water (55:0.05:45)

Solution A: Acetonitrile, trifluoroacetic acid, and water (4:0.005:6). [NOTE—Use only freshly-opened trifluoroacetic acid, ≤6 months.]

Solution B: Acetonitrile, trifluoroacetic acid, and water (8:0.005:2). [NOTE—Use only freshly-opened trifluoroacetic acid, ≤6 months.]

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
40	0	100
45	0	100
45.1	100	0
50	100	0

Standard solution: 1.25 µg/mL of USP Efavirenz RS in *Diluent*

Sample solution: 250 µg/mL of Efavirenz in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

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

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5 for efavirenz

Relative standard deviation: NMT 5.0% for efavirenz

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each of the three specified impurities in the portion of Efavirenz taken:

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

r_U = peak response for each of the three specified impurities from the *Sample solution*

r_S = peak response for efavirenz from the *Standard solution*

C_S = concentration of USP Efavirenz RS in the *Standard solution* (µg/mL)

C_U = concentration of Efavirenz in the *Sample solution* (µg/mL)

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

Acceptance criteria

Individual impurities: See *Impurity Table 2*. [NOTE—Disregard any peak less than 0.05%.]

Impurity Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Efavirenz	1.0	1.0	—
Efavirenz pent-3-ene-1-yne (*trans*)[a]	1.10	1.1	0.10
Efavirenz pent-3-ene-1-yne (*cis*)[b]	1.13	1.1	0.10
Efavirenz penteneyne[c]	1.14	1.0	0.10

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

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

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

SPECIFIC TESTS

- **COMPLETENESS OF SOLUTION ⟨641⟩:** Meets the requirements

  Solvent: Methanol

  Sample solution: 50 mg/mL of Efavirenz in *Solvent*

- **WATER DETERMINATION, *Method Ic*⟨921⟩**

  Sample: 100 mg/mL of Efavirenz in methanol

  Acceptance criteria: NMT 0.5%

- **ENANTIOMERIC PURITY**

  Mobile phase: Hexane and absolute alcohol (97:3)

  Retention time solution: 1 mg/mL of USP Efavirenz RS in *Mobile phase*

  Standard solution: 10 µg/mL of USP Efavirenz Racemic RS in *Mobile phase*

  Sample solution: 1 mg/mL of Efavirenz in *Mobile phase*

  Chromatographic system

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

  Mode: LC

  Detector: UV 250 nm

  Column: 4.6-mm × 25-cm column; 5-µm packing L10 connected in-line and before 4.6-mm × 25-cm column; 10-µm packing L40

  Column temperature: 35°

  Flow rate: 1.0 mL/min

  Injection size: 20 µL

  System suitability

  Samples: *Standard solution* and *Retention time solution*

  Suitability requirements

  Efavirenz identification: Identify the (*S*)-efavirenz enantiomer peak, *Retention time solution*

  Resolution: NLT 3.0 between (*R*)-efavirenz enantiomer and (*S*)-efavirenz enantiomer, *Standard solution*

  Relative standard deviation: NMT 5.0% for (*R*)-efavirenz enantiomer

  Analysis

  Samples: *Retention time solution*, *Standard solution*, and *Sample solution*

  [NOTE—Verify the identification of the efavirenz peak based on the chromatogram of the *Retention time solution*. The relative retention times for (*R*)-efavirenz enantiomer and (*S*)-efavirenz enantiomer are 0.88 and 1.00, respectively.]

  Calculate the percentage of (*R*)-efavirenz enantiomer in the portion of Efavirenz taken:

$$\text{Result} = 100 \times [r_R/(r_R + r_S)]$$

r_R = peak response of (*R*)-efavirenz enantiomer from the *Sample solution*

r_S = peak response of (*S*)-efavirenz enantiomer from the *Sample solution*

Acceptance criteria: NMT 0.5% of (*R*)-efavirenz enantiomer

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, protected from light, and store 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

USP Efavirenz Racemic RS

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

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

Chromatographic Database Information: Chromatographic Database

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