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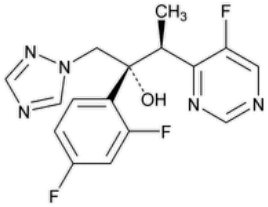
Voriconazole



$C_{16}H_{14}F_3N_5O$ 349.31

4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1*H*-1,2,4-triazol-1-ylmethyl)-, (α*R*,β*S*)-;

(α*R*,β*S*)-α-(2,4-Difluorophenyl)-5-fluoro-β-methyl-α-(1*H*-1,2,4-triazol-1-ylmethyl)-4-pyrimidineethanol CAS RN®: 137234-62-9; UNII: JFU09I87TR.

DEFINITION

Voriconazole contains NLT 97.5% and NMT 102.0% of Voriconazole ($C_{16}H_{14}F_3N_5O$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

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

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of *System suitability solution A*, as obtained in the test for *Voriconazole Related Compound B*.

ASSAY

• **Procedure**

Buffer: 1.9 g/L of ammonium formate in water. Adjust with formic acid to a pH of 4.0.

Mobile phase: Acetonitrile, methanol, and *Buffer* (15:30:55)

Standard solution: 25 µg/mL of USP Voriconazole RS in *Mobile phase*. [Note—Sonicate to dissolve, if necessary.]

Sample solution: 25 µg/mL of Voriconazole in *Mobile phase*. [Note—Sonicate to dissolve, if necessary.]

Chromatographic system

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

Mode: LC

Detector: UV 256 nm

Column: 3.9-mm × 15-cm; 4-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Column efficiency: NLT 3500 theoretical plates

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of voriconazole ($C_{16}H_{14}F_3N_5O$) in the portion of Voriconazole taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 97.5%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Voriconazole Related Compounds C and D**

Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: 0.25 µg/mL of USP Voriconazole RS in *Mobile phase*

Standard solution: 2.5 µg/mL each of USP Voriconazole RS, USP Voriconazole Related Compound C RS, and USP Voriconazole Related Compound D RS in *Mobile phase*. [Note—Sonicate to dissolve, if necessary.]

Sample solution: 500 µg/mL of Voriconazole in *Mobile phase*. [Note—Sonicate to dissolve, if necessary.]

System suitability

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

Suitability requirements

Tailing factor: NMT 2.0 for the voriconazole peak, *Standard solution*

Column efficiency: NLT 3500 theoretical plates for the voriconazole peak, *Standard solution*

Relative standard deviation: NMT 10.0%, *System suitability solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of voriconazole related compound C and voriconazole related compound D in the portion of Voriconazole taken:

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

r_U = peak response of voriconazole related compound C or voriconazole related compound D from the *Sample solution*

r_S = peak response of voriconazole related compound C or voriconazole related compound D from the *Standard solution*

C_S = concentration of USP Voriconazole Related Compound C RS or USP Voriconazole Related Compound D RS in the *Standard solution* (µg/mL)

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

Calculate the percentage of any unspecified impurity in the portion of Voriconazole taken:

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

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

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

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

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

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Voriconazole related compound C[a]	0.26	0.2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Voriconazole related compound D[b]	0.61	0.1
Voriconazole	1.0	—
Any unspecified impurity[c]	—	0.1
Total impurities[d]	—	0.5

[a] 1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone.

[b] (2*RS*,3*SR*)-2-(2,4-Difluorophenyl)-3-(pyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol.

[c] Disregard peaks less than 0.05%.

[d] Include voriconazole related compound B and voriconazole related compound F.

- **Voriconazole Related Compound F**

Sodium hydroxide solution: 470 g/L of sodium hydroxide in water

Mobile phase: Methanol, water, and *Sodium hydroxide solution* (500: 1500: 0.175). [Note—Minimize the carbonate formation in the *Mobile phase* by degassing methanol and water before mixing.]

Suppressant solution: 12 mM of sulfuric acid in water

Chloride stock solution: 85 µg/mL of sodium chloride in water

Standard stock solution: 250 µg/mL of USP Voriconazole Related Compound F RS. Dissolve in 50% of the final volume with methanol, and dilute with *Mobile phase* to volume.

Standard solution: 5 µg/mL of USP Voriconazole Related Compound F RS from the *Standard stock solution* in a mixture of methanol and *Mobile phase* (50:50)

System suitability solution A: 5 µg/mL of USP Voriconazole Related Compound F RS from the *Standard stock solution* and 1.7 µg/mL of sodium chloride in a mixture of methanol and *Mobile phase* (50:50)

System suitability solution B: 2.5 µg/mL of USP Voriconazole Related Compound F RS from the *Standard solution* in *Mobile phase*

Sample solution: 5 mg/mL of Voriconazole. Dissolve in 50% of the final volume with methanol, and dilute with *Mobile phase* to volume.

Chromatographic system

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

Mode: Ion chromatography/LC

Detector: Conductivity with anion suppressor

Column: 4-mm × 5-cm guard column and 4-mm × 25-cm analytical column; both packing L46

Column temperature: 40°

Flow rate: 1 mL/min

Flow rate (for anion suppressor): 2 mL/min

Injection size: 20 µL

System suitability

Samples: *System suitability solution A* and *System suitability solution B*

[Note—The relative retention times for acetate ion (for information only), voriconazole related compound F, and chloride ion are 0.47, 1.0, and 1.5, respectively.]

Suitability requirements

Resolution: NLT 3.5 between the voriconazole related compound F and chloride peaks, *System suitability solution A*

Tailing factor: NMT 2.0, *System suitability solution B*

Relative standard deviation: NMT 10.0%, *System suitability solution B*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of voriconazole related compound F in the portion of Voriconazole taken:

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

r_U = peak response of voriconazole related compound F from the *Sample solution*

r_S = peak response of voriconazole related compound F from the *Standard solution*

C_S = concentration of USP Voriconazole Related Compound F RS in the *Standard solution* (µg/mL)

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

Acceptance criteria: NMT 0.1%

• **Voriconazole Related Compound B**

Initially dissolve the Standard and sample materials in 4% of the final volume of acetonitrile.

Buffer: 0.8 g/L of ammonium acetate. Adjust with glacial acetic acid to a pH of 5.0.

Mobile phase: Acetonitrile and *Buffer* (18:82)

System suitability solution A: 500 µg/mL of USP Voriconazole RS and 2.5 µg/mL of USP Voriconazole Related Compound B in *Mobile phase*.

System suitability solution B: 0.25 µg/mL of USP Voriconazole Related Compound B RS in *Mobile phase*

Standard solution: 2.5 µg/mL of USP Voriconazole Related Compound B RS in *Mobile phase*

Sample solution: 500 µg/mL of Voriconazole in *Mobile phase*.

Chromatographic system

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

Mode: LC

Detector: UV 256 nm

Column: 4.6-mm × 25-cm; 5-µm packing L45

Column temperature: 30°

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Samples: *System suitability solution A* and *System suitability solution B*

[Note—The relative retention times for voriconazole and voriconazole related compound B are 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 4.0 between the voriconazole and voriconazole related compound B peaks, *System suitability solution A*

Tailing factor: NMT 2.0 for the voriconazole related compound B peak, *System suitability solution A*

Relative standard deviation: NMT 10.0%, *System suitability solution B*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of voriconazole related compound B in the portion of Voriconazole taken:

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

r_U = peak response of voriconazole related compound B from the *Sample solution*

r_S = peak response of voriconazole related compound B from the *Standard solution*

C_S = concentration of USP Voriconazole Related Compound B RS in the *Standard solution* (µg/mL)

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

Acceptance criteria: NMT 0.2%

SPECIFIC TESTS

• **Bacterial Endotoxins Test ⟨85⟩:** Where the label states that Voriconazole is sterile or that it must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.2 USP Endotoxin Units/mg of voriconazole.

• **Sterility Tests ⟨71⟩:** Where the label states that Voriconazole is sterile, it meets the requirements.

• **Water Determination, *Method I* ⟨921⟩:** NMT 0.4%

ADDITIONAL REQUIREMENTS

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

• **Labeling:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP Reference Standards ⟨11⟩**

USP Voriconazole RS

USP Voriconazole Related Compound B RS

(2*S*,3*R*)-2-(2,4-Difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol.

$C_{16}H_{14}F_3N_5O$ 349.31

USP Voriconazole Related Compound C RS

1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone.

$C_{10}H_7N_3OF_2$ 223.18

USP Voriconazole Related Compound D RS

(2*RS*,3*SR*)-2-(2,4-Difluorophenyl)-3-(pyrimidin-4-yl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol.

$C_{16}H_{15}F_2N_5O$ 331.32

USP Voriconazole Related Compound F RS

{(1*RS*,4*SR*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl}methanesulfonic acid.

$C_{10}H_{16}O_4S$ 232.30

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

Topic/Question	Contact	Expert Committee
VORICONAZOLE	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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