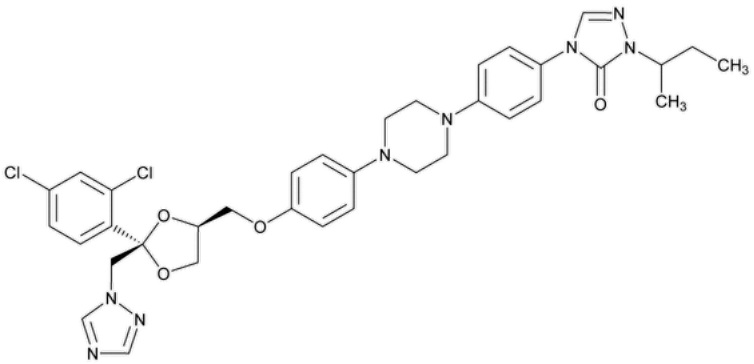
Status: Currently Official on 18-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-DEF4FB08-751A-4EB2-A94B-0FEE17605BA3_4_en-US
DOI: https://doi.org/10.31003/USPNF_M43724_04_01
DOI Ref: 5a0pe

Itraconazole



$C_{35}H_{38}Cl_2N_8O_4$ 705.63

3*H*-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-;
(±)-1-*sec*-Butyl-4-[*p*-[4-[*p*-[[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one CAS RN®: 84625-61-6; UNII: 304NUG5GF4.

DEFINITION

Itraconazole contains NLT 98.0% and NMT 102.0% of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

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

• **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**

Prepare the solutions containing itraconazole immediately before use.

Solution A: 13.6 g/L of tetrabutylammonium hydrogen sulfate in water

Solution B: Acetonitrile

Diluent: Dilute 4.0 mL of hydrochloric acid with methanol to 1 L.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
12	50	50
16	80	20
20	80	20

Standard solution: 0.3 mg/mL of USP Itraconazole RS in *Diluent*

Sample solution: 0.3 mg/mL of Itraconazole in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of itraconazole ($C_{35}H_{38}Cl_2N_8O_4$) in the portion of Itraconazole taken:

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

r_U = peak response of itraconazole from the *Sample solution*

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

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

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

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition** ⟨281⟩

Sample: 1.0 g

Acceptance criteria: NMT 0.1%

• **Organic Impurities**

Solution B, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.

Solution A: 27.2 g/L of tetrabutylammonium hydrogen sulfate in water

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
2	80	20
22	50	50
27	50	50

System suitability solution: 10 mg/mL of USP Itraconazole System Suitability Mixture RS in *Diluent*

Standard solution: 10.0 µg/mL of USP Itraconazole RS in *Diluent*

Sample solution: 10 mg/mL of Itraconazole in *Diluent*

System suitability

Sample: *System suitability solution*

Suitability requirements

Peak-to-valley ratio: NLT 1.5

Calculate the peak-to-valley ratio (*p/v*), using the following:

$$p/v = H_p/H_v$$

H_p = height above the baseline of the peak due to the *n*-butyl isomer impurity

H_v = height above the baseline of the lowest point of the curve separating this peak from the itraconazole peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Itraconazole taken:

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

r_U = peak response of each impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 3*. Disregard any peak less than 0.05%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
4-Methoxy derivative[a]	0.20	0.5
4-Triazolyl isomer[b]	0.74	0.5
Propyl analog[c]	0.86	0.5
Isopropyl analog[d]	0.86	0.5
Epimer[e]	0.93	0.5
Itraconazole	1.0	—
n-Butyl isomer[f]	1.05	0.5
Didioxolanyl analog[g]	1.3	0.5
Any unspecified impurity	—	0.10
Total impurities	—	1.25

[a] 2-*sec*-Butyl-4-{4-[4-(4-methoxyphenyl)piperazin-1-yl]phenyl}-2*H*-1,2,4-triazol-3(4*H*)-one.

[b] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(4*H*-1,2,4-Triazol-4-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-*sec*-butyl-2*H*-1,2,4-triazol-3(4*H*)-one.

[c] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-propyl-2*H*-1,2,4-triazol-3(4*H*)-one.

[d] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-isopropyl-2*H*-1,2,4-triazol-3(4*H*)-one.

[e] 4-(4-{4-[4-({(2*RS*,4*RS*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-*sec*-butyl-2*H*-1,2,4-triazol-3(4*H*)-one.

[f] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-butyl-2*H*-1,2,4-triazol-3(4*H*)-one.

[g] 4-(4-{4-[4-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-2-({(2*RS*,4*SR*)-2-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl}methyl)-2*H*-1,2,4-triazol-3(4*H*)-one.

SPECIFIC TESTS

- **Optical Rotation** ⟨781A⟩, *Procedures, Angular Rotation*

  Sample: 100 mg/mL in methylene chloride. [Note—Use methylene chloride to zero the instrument.]

  Acceptance criteria: −0.10° to +0.10° at 20°

- **Loss on Drying** ⟨731⟩

  Sample: Dry 1 g at 105° for 4 h.

  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at room temperature.
- **USP Reference Standards** ⟨11⟩

USP Itraconazole RS

USP Itraconazole System Suitability Mixture RS

This mixture contains itraconazole and six other minor components (4-triazolyl isomer, propyl analog, isopropyl analog, epimer, *n*-butyl isomer, and didioxolanyl analog).

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

Topic/Question	Contact	Expert Committee
ITRACONAZOLE	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

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(6)

Current DocID: GUID-DEF4FB08-751A-4EB2-A94B-0FEE17605BA3_4_en-US

DOI: https://doi.org/10.31003/USPNF_M43724_04_01

DOI ref: 5a0pe