Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Dec-2024
Document Type: USP Monographs
DocId: GUID-31704F3F-3AAE-4D75-B40F-7E4A195ADA31_2_en-US
DOI: https://doi.org/10.31003/USPNF_M44000_02_01
DOI Ref: m4g65

Ketoconazole Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-notice-ketoconazole-tabs-20241122.

DEFINITION
Ketoconazole Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$).

IDENTIFICATION
• **A.**
Standard solution: 1 mg/mL of USP Ketoconazole RS in chloroform
Sample solution: Nominally 1 mg/mL of ketoconazole in chloroform prepared as follows. Transfer a quantity of finely powdered Tablets, equivalent to 50 mg of ketoconazole, to a suitable flask. Add 50 mL of chloroform, shake for 2 min, and filter.
Chromatographic system
(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)
Mode: TLC
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture
Application volume: 10 µL
Developing solvent system: *n*-Hexane, ethyl acetate, methanol, glacial acetic acid, and water (42:40:15:1:2)
Analysis: Allow the spots to dry, and develop the chromatogram in the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the chamber, air-dry, and view under short-wavelength UV light.
Acceptance criteria: The R_F value of the principal spot of the *Sample solution* corresponds to that of the *Standard solution*.

ASSAY
• **Procedure**
Solution A: Diisopropylamine in methanol (1 in 500)
Solution B: 5 mg/mL of ammonium acetate in water
Mobile phase: *Solution A* and *Solution B* (7:3)
Diluent: Methanol and methylene chloride (1:1)
Internal standard solution: 5 mg/mL of USP Terconazole RS in *Diluent*
Standard solution: 0.4 mg/mL of USP Ketoconazole RS in *Diluent* prepared as follows. Transfer 20 mg of USP Ketoconazole RS to a 50-mL volumetric flask. Add 5.0 mL of *Internal standard solution*, and dilute with *Diluent*.
Sample stock solution: Nominally 4 mg/mL of ketoconazole in *Diluent* prepared as follows. Weigh and finely powder NLT 20 Tablets. Transfer the nominal equivalent to 200 mg of ketoconazole to a suitable screw-capped bottle. Add 50.0 mL of *Diluent*, shake by mechanical means for 30 min, and centrifuge.
Sample solution: Nominally 0.4 mg/mL of ketoconazole in *Diluent* prepared as follows. Transfer 5.0 mL of the clear supernatant so obtained from the *Sample stock solution* to a 50-mL volumetric flask. Add 5.0 mL of *Internal standard solution*, and dilute with *Diluent* to volume.
Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 3.9-mm × 30-cm; packing L1
Flow rate: 3 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
[Note—The relative retention times for ketoconazole and terconazole are 0.6 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between ketoconazole and terconazole
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$) in the portion of Tablets taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = peak response ratio of ketoconazole to terconazole from the *Sample solution*

R_S = peak response ratio of ketoconazole to terconazole from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution ⟨711⟩**

▲**Test 1**▲ (RB 1-Dec-2024)

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Analytical wavelength: UV 270 nm

Standard solution: USP Ketoconazole RS in *Medium*

Sample solutions: Pass portions of the solution under test through a suitable filter of 0.45-µm pore size, and dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Tolerances: NLT 80% (*Q*) of the labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Simulated gastric fluid TS without pepsin; 800 mL

Apparatus 1: 100 rpm

Time: 15 min

Solution A: Add 2.0 mL of diisopropylamine to 1 L of methanol.

Solution B: Dissolve 5 g of ammonium acetate in 1 L of water.

Mobile phase: *Solution A* and *Solution B* (70:30)

Standard solution: 0.25 mg/mL of USP Ketoconazole RS in *Medium*. Sonicate to dissolve, if necessary.

Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of ketoconazole

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$) dissolved:

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

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

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

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

V = volume of *Medium*, 800 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$) is dissolved.▲ (RB 1-Dec-2024)

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

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

Add the following:

▲• **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-Dec-2024)

• **USP Reference Standards** ⟨11⟩

USP Ketoconazole RS

USP Terconazole RS

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

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

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 30(4)

Current DocID: GUID-31704F3F-3AAE-4D75-B40F-7E4A195ADA31_2_en-US

DOI: https://doi.org/10.31003/USPNF_M44000_02_01

DOI ref: m4g65