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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 μ L

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 $\times$ 30-cm; packing [L1](#)

Flow rate: 3 mL/min

Injection volume: 20 μ L

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

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