**Ketoconazole (Ketoconazolum)**

\[ \text{C}_{26}\text{H}_{28}\text{Cl}_{2}\text{N}_{4}\text{O}_{4} \]

**Relative molecular mass.** 531.4

**Chemical name.** ±-cis-1-Acetyl-4-\[p-(2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy]phenyl\]piperazine; cis-1-acetyl-4-\[4-(2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy]phenyl\]piperazine; cis-1-acetyl-4-\[p-(2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy]phenyl\]piperazine; CAS Reg. No. 65277-42-1.

**Description.** A white or almost white powder.

**Solubility.** Practically insoluble in water; freely soluble in dichloromethane R; soluble in methanol R; sparingly soluble in ethanol (~750 g/l) TS.

**Category.** Antifungal drug.

**Storage.** Ketoconazole should be kept in a well-closed container, protected from light.

**Requirements**

Ketoconazole contains not less than 99.0% and not more than the equivalent of 101.0% of \( \text{C}_{26}\text{H}_{28}\text{Cl}_{2}\text{N}_{4}\text{O}_{4} \), calculated with reference to the dried substance.

**Identity tests**

- Either test A alone or tests B, C, and D may be applied.

  A. Carry out the examination as described under **1.7 Spectrophotometry in the infrared region.** The infrared absorption spectrum is concordant with the spectrum obtained from ketoconazole RS or with the reference spectrum of ketoconazole.

  B. See the test described below under "Related substances". The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

  C. Place 1 mL of nitric acid (~1000 g/l) TS in a porcelain dish and add 10 mg of the substance; a clear orange-red solution is produced.

  D. Place 30 mg in a porcelain dish, add 0.3 g of anhydrous sodium carbonate R, and heat over an open flame for 10 minutes. Allow to cool, add 5 mL of nitric acid (~130 g/l) TS to the residue, stir, and filter. To 1 mL of the filtrate add 1 mL of water. The solution yields reaction A described under **2.1 General identification tests** as characteristic of chlorides.

**Melting range.** 148-152°C.

**Heavy metals.** Use 1.0 g for the preparation of the test solution as described under **2.2.3 Limit test for heavy metals, Procedure 3;** determine the heavy metals content according to Method A; not more than 20 mg/g.

**Sulfated ash.** Not more than 1.0 mg/g.

**Loss on drying.** Dry to constant mass at 105 °C; it loses not more than 5 mg/g.

**Related substances.** Carry out the test as described under **1.14.1 Thin-layer chromatography**, using silica gel R1 as the coating.
substance and a mixture of 4 volumes of dioxan R, 4 volumes of methanol R, and 2 volumes of ammonium acetate TS as the mobile phase. Apply separately to the plate 5μl of each of 5 solutions in the mobile phase containing (A) 6mg of Ketoconazole per mL, (B) 6 mg of ketoconazole RS per mL, for (C) prepare a mixture of 6 mg of each of ketoconazole RS and econazole nitrate RS per mL, (D) 30 μg of ketoconazole RS per mL, and (E) 15 μg of ketoconazole RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air for 15 minutes. Expose the plate to iodine vapours until the spots appear and examine the chromatogram in daylight.

The test is not valid unless solution C shows two clearly separated spots. Any spot obtained with solution A, other than the principal spot, is not more intense than the principal spot obtained with solution D (0.5%) and only one such spot is more intense than that obtained with solution E (0.25%).

**Assay.** Dissolve about 0.2 g, accurately weighed, in 70 mL of a mixture of 1 volume of glacial acetic acid R1 and 7 volumes of ethylmethylketone R, and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A, determining the end-point potentiometrically.

Each mL of perchloric acid (0.1 mol/l) VS is equivalent to 26.57mg of \( C_{26}H_{28}Cl_2N_4O_4 \).