

Ketoconazole

Antifungal Class:

Azoles

Antifungal Spectrum:

Opportunistic yeasts: *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Cryptococcus neoformans*, *Candida krusei* (variable activity)

Opportunistic hyaline moulds: *Scedosporium spp.* (variable activity)

Dimorphic moulds: *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Parracoccidioides brasiliensis*, *Sporothrix schenckii*, *Penicillium marneffeii*

Dematiaceous moulds: variable activity

Mechanism of Action:

Inhibition of 14- α -demethylase blocks formation of ergosterol and leads to the buildup of toxic methylated 14- α -sterols and depletes ergosterol in the cell membrane.

Pharmacodynamics:

Other azoles have shown in murine models to exhibit AUC:MIC ratio as predictive of effect for *Candida spp.* This may vary by fungal species however.

Pharmacokinetics:

Tmax: 1-4 hours; Cmax:3-5mcg/ml; Vd: 1.16 L/Kg; Total Clearance: 2.75 ml/min/Kg; Table 2

Adverse Effects:

Gastrointestinal: nausea, vomiting, abdominal pain, anorexia

Skin and appendages pruritus, rash, potentially exfoliative

Liver and biliary system: Elevation of hepatic transaminases (<10%), hepatitis

Immunologic: anaphylaxis

Endocrine: adrenal insufficiency, decreased testosterone synthesis, menstrual irregularities

Special senses: photophobia

Nervous System: headache

Dosage:

Cream, topical: 2% (15g, 30g, 60g)

Shampoo, topical: 1% (6mL, 120 mL, 210mL)

Tablet: 200 mg

Mucosal infections/cutaneous infection: 200 mg/day for 2 weeks

Extensive mucosal infection/recalcitrant dermatophyte infections: 400 mg/day for 4 weeks

Systemic mycoses: 400 mg/day for 6-12 months

Shampoo: Apply twice weekly for 4 weeks with at least 3 days between each shampoo.

Topical: Rub gently into the affected area once daily to twice daily.

Disease state based dosing:

Renal failure: Dose adjustment is unnecessary in patients with altered renal function.

Hepatic failure: Dose adjustment is unnecessary in patients with moderate hepatic dysfunction.

Contraindications/Warnings/Precautions:

Contraindications: hypersensitivity to ketoconazole; CNS fungal infections (due to poor CNS penetration); coadministration with ergot derivatives, astemizole, or cisapride is contraindicated due to risk of potentially fatal cardiac arrhythmias

Drug Interactions:

Ketoconazole is a potent inhibitor of the cytochrome P450 3A4 isoenzyme system. Caution should be exercised and monitoring is suggested when concomitantly administering ketoconazole with drugs that have narrow therapeutic windows and are substrates of the CYP3A4 substrates.

Table 4

Pregnancy:

Category C: Risk unknown. Human studies inadequate.

Monitoring Requirements:

Liver function tests should be monitored throughout treatment.

Brand names/Manufacturer: Several brand names/manufacturers