ORAZOLE

Tablets

Composition

Each tablet contains Ketoconazole 200 mg.

Action

Ketoconazole is a synthetic imidazole dioxolane derivative with a fungicidal or fungistatic activity against dermatophytes, yeasts (*Candida, Pityrosporum, Torulopsis, and Cryptococcus*), dimorphic fungi and eumycetes. Ketoconazole is less sensitive to *Aspergillus spp., Sporothrix schenckii,* some *Dematiaceae, Mucor spp.* and other phycomycetes, except *Entomophthorales.*
Ketoconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the membrane.

Pharmacokinetics

The bioavailability of Ketoconazole is dependent on the presence of an acidic pH for dissolution and absorption. Peak plasma levels of 1.6-6.9 mcg/ml occur within 1-2 hours after a single 200 mg oral dose taken with a meal (which may improve bioavailability). In vitro, plasma protein binding is about 95-99%, mainly to albumin. At recommended doses, cerebrospinal fluid penetration is negligible. Plasma elimination is biphasic, with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Ketoconazole undergoes extensive hepatic metabolism; resultant metabolites are inactive. The major route of excretion is enterohepatic; 85-90% of the drug excreted in the bile and feces. About 10-15% of the dose excreted in the urine, 2-4% as unchanged drug.

Indications

Treatment

Orazole is indicated in the treatment of superficial and deep mycosis in adults and children, as follows:

- Systemic mycoses e.g. systemic candidiasis, paracoccidioidomycosis, coccidioidomycosis, histoplasmosis.
- Serious chronic mucocutaneous candidiasis (including exceptionally disabling Candida paronychia) not responsive to other therapy, or when the organism is resistant to other therapy.
- Serious mycoses of the gastrointestinal tract not responsive to other therapy, or when the organism is resistant to other therapy.
- Chronic vaginal candidiasis not responsive to other therapy.
- Culturally-confirmed dermatophyte infections of the skin and finger nails which have failed to respond to adequate dosage regimens of conventional antidermatophyte agents, excluding pityriasis versicolor and fungus infections of toe nails.

Prophylaxis

Prophylactic treatment to prevent mycotic infection in carefully selected cases where a long-term immunosuppressive response is expected.

Contraindications

- Ketoconazole is contra-indicated in patients who have shown hypersensitivity to it or any of its ingredients.
- Ketoconazole should not be given to patients with pre-existing liver disease.
- Ketoconazole is not recommended during pregnancy, as ketoconazole has been shown to be teratogenic in animals.
- Breastfeeding mothers should not use Ketoconazole.
- Ketoconazole is not intended for use in children, as safety has not been proven.
- The concomitant administration of terfenadine and astemizole with Ketoconazole is contra-indicated.

Warnings

Patients taking Ketoconazole should avoid alcohol. Cases have been reported of a disulfiram-like reaction to alcohol, characterized by flushing, peripheral oedema, nausea, and headache.

Hepatitis has been reported during treatment with Ketoconazole. If symptoms or signs suggestive of hepatic dysfunction detected, medication should be stopped at once. Patients on Ketoconazole should be instructed to report any of the prodromal symptoms of hepatitis, such as fatigue associated with nausea or vomiting, jaundice, dark urine or pale stools, immediately and stop treatment.

Factors increasing the risk of hepatitis are females over 50 years of age, previous treatment with griseofulvin, history of liver disease, known drug intolerance, long-lasting treatment, and concomitant use of liver compromising medication.

Patients on prolonged therapy (longer than 2 weeks) should have regular monitoring of liver function (before treatment, after 2 weeks and, later on, monthly), particularly those patients with a known history of prior liver disease, or an idiosyncrasy to other medicines.

Should liver disease be confirmed, the therapy is to be discontinued. It should be noted, however, that in patients with fungal infections, whether they are treated with Ketoconazole or not, a mild transient asymptomatic increase of transaminase or alkaline phosphatase may occur. In most instances, enzyme levels return to normal without the need to discontinue medication. After long-term griseofulvin treatment, it is advisable to wait for one month before starting treatment with Ketoconazole.

Pregnancy
Category C
Ketoconazole contraindicated in pregnancy.
It has been used without harm to treat vaginal candidiasis during pregnancy

Nursing Mothers
Although it is unknown whether the drug is excreted in human breast milk, risk/benefit should be taken into account if ketoconazole is considered for use in nursing mothers.

Adverse Reactions
Nausea, vomiting, gastro-intestinal complaints, constipation, headache, dizziness, somnolence or drowsiness, photophobia, paraesthesia, thrombocytopenia, exanthema or itching has been reported. Increases in serum liver enzymes may occur. Anaphylactoid reactions, alopecia, urticaria, rash, transient decreased libido, reversible gynecomastia and oligospermia may occur.

Decreased plasma testosterone values that normalize within 24 hours after administration of Ketoconazole may also occur. During long-term therapy at this level of dosage, testosterone levels are usually not significantly different from controls.

Precautions
Serum cortisol levels may decrease and response of cortisol on ACTH may be blunted. The adrenal function should therefore be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc.).

Drug Interactions
Drugs affecting the metabolism of ketoconazole
Enzyme inducing drugs such as rifampicin, rifabutin, carbamazepine, isoniazid, and phenytoin significantly reduce the bioavailability of ketoconazole.
Drugs that affect the gastric acidity: See under “Warnings”.
Ritonavir increases the bioavailability of ketoconazole. Therefore, when given concomitantly, a dose reduction of ketoconazole should be considered.

Effect of ketoconazole on the metabolism of other drugs
Ketoconazole can inhibit the metabolism of drugs metabolised by certain hepatic P450 enzymes, especially of the CYP 3A family. This can result in an increase and/or prolongation of their effects including side effects.
Examples are:

Drugs which should not be used during treatment with ketoconazole
Terfenadine, astemizole, mizolastine, cisapride, triazolam, oral midazolam, dofetilide, quinidine, pimozide, CYP3A4 metabolised HMG-Co A reductase inhibitors such as simvastatin and lovastatin.

Drugs whose plasma levels, effects, or side effects should be monitored. Their dosage should be reduced if necessary
Oral Anticoagulants; HIV Protease Inhibitors such as indinavir, saquinavir; Certain Antineoplastic Agents such as vinca alkaloids, busulphan and docetaxel; CYP3A4 metabolised Calcium Channel Blockers such as dihydropropyridines and probably verapamil.

Certain immunosuppressive Agents: cyclosporine, tacrolimus rapamycin = sirolimus;

Others: digoxin, carbamazepine, buspirone, alfentanil, sildenafil, alprazolam, brotizolam, midazolam IV, rifabutin, methyl prednisolone and trimetrexate, ebastine, reboxetine. Cases have been reported of a disulfiram-like reaction to alcohol, characterized by flushing, peripheral oedema, nausea, and headache.

Dosage and Administration

Chronic and recurrent vaginal candidiasis not responding to topical treatment
Two tablets (400 mg) once daily with a meal for 5 days.

All other indications
One tablet (200 mg) once daily with a meal until at least one week after the symptoms have disappeared and until all cultures have become negative. The dose of ketoconazole may be doubled to 400 mg if the clinical response is insufficient after a reasonable period of treatment.

The usual duration of treatment is a follows:

Serious chronic mycoses of the skin and hair:	1 - 2 months
Systemic candidiasis:	1 - 2 months
Serious chronic mucocutaneous candidiasis:	6 - 12 months
Paracoccidioidomycosis and histoplasmosis:	2 - 6 months
Dermatophytes:	4 weeks

Note: Orazole should be taken with meals for maximal absorption. Effective absorption depends upon intact gastric activity; hence, concomitant administration with drugs that reduce gastric secretion (anticholinergic drugs, antacids, and H_2 blockers) should be avoided. When indicated, these drugs should not be taken within two hours after Orazole.

Prophylaxis
Prophylactic treatment should be administered for as long as an increased risk of mycotic infection exists. The adult dosage is 400 mg daily. The paediatric dosage is 4-8 mg/kg body weight daily.

Over Dosage

In the event of over dosage, patients should be treated symptomatically with supportive measures or gastric lavage, as necessary.

Presentation

Box of 10 tablets.