JANSSEN
PHARMACEUTICALS

NIZORAL®
(KETOCONAZOLE)
TABLETS

WARNING:

NIZORAL® Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

Hepatotoxicity

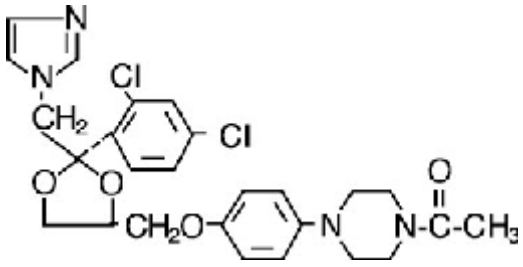
Serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation has occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See WARNINGS section.

QT Prolongation and Drug Interactions Leading to QT Prolongation

Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, cisapride. Ketoconazole can cause elevated plasma concentrations of these drugs and may prolong QT intervals, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions sections.

DESCRIPTION

NIZORAL® is a synthetic broad-spectrum antifungal agent available in scored white tablets, each containing 200 mg ketoconazole base for oral administration. Inactive ingredients are colloidal silicon dioxide, corn starch, lactose, magnesium stearate, microcrystalline cellulose, and povidone. Ketoconazole is cis-1- acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxyl]phenyl] piperazine and has the following structural formula:



Ketoconazole is a white to slightly beige, odorless powder, soluble in acids, with a molecular weight of 531.44.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Mean peak plasma levels of approximately 3.5 µg/mL are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal. Subsequent plasma elimination is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. Following absorption from the gastrointestinal tract, NIZORAL® is converted into several inactive metabolites. The major identified metabolic pathways are oxidation and degradation of the imidazole and piperazine rings, oxidative O-dealkylation and aromatic hydroxylation. About 13% of the dose is excreted in the urine, of which 2 to 4% is unchanged drug. The major route of excretion is through the bile into the intestinal tract. *In vitro*, the plasma protein binding is about 99% mainly to the albumin fraction. Only a negligible proportion of ketoconazole reaches the cerebrospinal fluid. Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption.

Electrocardiogram

Pre-clinical electrophysiological studies have shown that ketoconazole inhibits the rapidly activating component of the cardiac delayed rectifier potassium current, prolongs the action potential duration, and may prolong the QT_c interval. Data from some clinical PK/PD studies and drug interaction studies suggest that oral dosing with ketoconazole at 200 mg twice daily for 3-7 days can result in an increase of the QT_c interval: a mean maximum increase of about 6 to 12 msec was seen at ketoconazole peak plasma concentrations about 1-4 hours after ketoconazole administration.

MICROBIOLOGY

Mechanism of Action

Ketoconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane.

Activity In Vitro & In Vivo

NIZORAL® Tablets are active against clinical infections with *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*.

INDICATIONS AND USAGE

NIZORAL® Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

NIZORAL® (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. NIZORAL® Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.

CONTRAINDICATIONS

Drug Interactions

Coadministration of a number of CYP3A4 substrates is contraindicated with NIZORAL® Tablets. Coadministration with ketoconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both therapeutic and adverse effects. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. See WARNINGS section, and PRECAUTIONS: Drug Interactions section for specific examples.

Liver Disease

The use of NIZORAL® Tablets is contraindicated in patients with acute or chronic liver disease.

Hypersensitivity

NIZORAL® is contraindicated in patients who have shown hypersensitivity to the drug.

WARNINGS

NIZORAL® Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

Hepatotoxicity

Serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation, has occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Serious hepatotoxicity was reported both by patients receiving high doses for short treatment durations and by patients receiving low doses for long durations.

The hepatic injury has usually, but not always, been reversible upon discontinuation of NIZORAL® Tablets treatment. Cases of hepatitis have been reported in children.

At baseline, obtain laboratory tests (such as SGGT, alkaline phosphatase, ALT, AST, total bilirubin (TBL), Prothrombin Time (PT), International Normalization Ratio (INR), and testing for viral hepatitides). Patients should be advised against alcohol consumption while on treatment. If possible, use of other potentially hepatotoxic drugs should be avoided in patients receiving NIZORAL® Tablets.

Prompt recognition of liver injury is essential. During the course of treatment, serum ALT should be monitored weekly for the duration of treatment. If ALT values increase to a level above the upper limit of normal or 30 percent above baseline, or if the patient develops symptoms, ketoconazole treatment should be interrupted and a full set of liver tests should be obtained. Liver tests should be repeated to ensure normalization of values. Hepatotoxicity has been reported with restarting oral ketoconazole (rechallenge). If it is decided to restart oral ketoconazole, monitor the patient frequently to detect any recurring liver injury from the drug.

QT Prolongation and Drug Interactions Leading to QT Prolongation

Ketoconazole can prolong the QT interval. Co-administration of the following drugs with ketoconazole is contraindicated: dofetilide, quinidine, pimozide, and cisapride. Ketoconazole can cause elevated plasma concentrations of these drugs which may prolong the QT interval, sometimes resulting in life-threatening ventricular dysrhythmias such as torsades de pointes.

Adrenal Insufficiency

NIZORAL® Tablets decrease adrenal corticosteroid secretion at doses of 400 mg and higher. This effect is not shared with other azoles. The recommended dose of 200 mg - 400 mg daily should not be exceeded.

Adrenal function should 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.).

Adverse Reactions Associated with Unapproved Uses

Ketoconazole has been used in high doses for the treatment of advanced prostate cancer and for Cushing's syndrome when other treatment options have failed. The safety and effectiveness of ketoconazole have not been established in these settings and the use of ketoconazole for these indications is not approved by FDA.

In a clinical trial involving 350 patients with metastatic prostatic cancer, eleven deaths were reported within two weeks of starting treatment with high doses of ketoconazole

tablets (1200 mg/day). It is not possible to ascertain from the information available whether death was related to ketoconazole therapy or adrenal insufficiency in these patients with serious underlying disease.

Hypersensitivity

Anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported.

Enhanced Sedation

Co-administration of NIZORAL® Tablets with oral midazolam, oral triazolam or alprazolam has resulted in elevated plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. Concomitant administration of NIZORAL® Tablets with oral triazolam, oral midazolam, or alprazolam is contraindicated. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions sections.)

Myopathy

Co-administration of CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin, and lovastatin is contraindicated with NIZORAL® Tablets. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions sections.)

PRECAUTIONS

General

NIZORAL® Tablets have been demonstrated to lower serum testosterone. Once therapy with NIZORAL® Tablets has been discontinued, serum testosterone levels return to baseline values. Testosterone levels are impaired with doses of 800 mg per day and abolished by 1600 mg per day. Clinical manifestations of decreased testosterone concentrations may include gynecomastia, impotence and oligospermia.

Information for Patients

Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, abdominal pain, jaundice, dark urine or pale stools (see WARNINGS section).

Drug Interactions

Drugs that affect the absorption, distribution, metabolism, and excretion of ketoconazole may alter the plasma concentrations of ketoconazole. For example, gastric acid suppressants (e.g., antacids, histamine H_2-blockers, proton pump inhibitors) have been shown to reduce plasma concentrations of ketoconazole.

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