

KETOCONAZOLE - ketoconazole tablet
STAT RX USA LLC

KETOCONAZOLE TABLETS USP, 200 mg
0900

WARNING

When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. See **WARNINGS** and **PRECAUTIONS** sections.

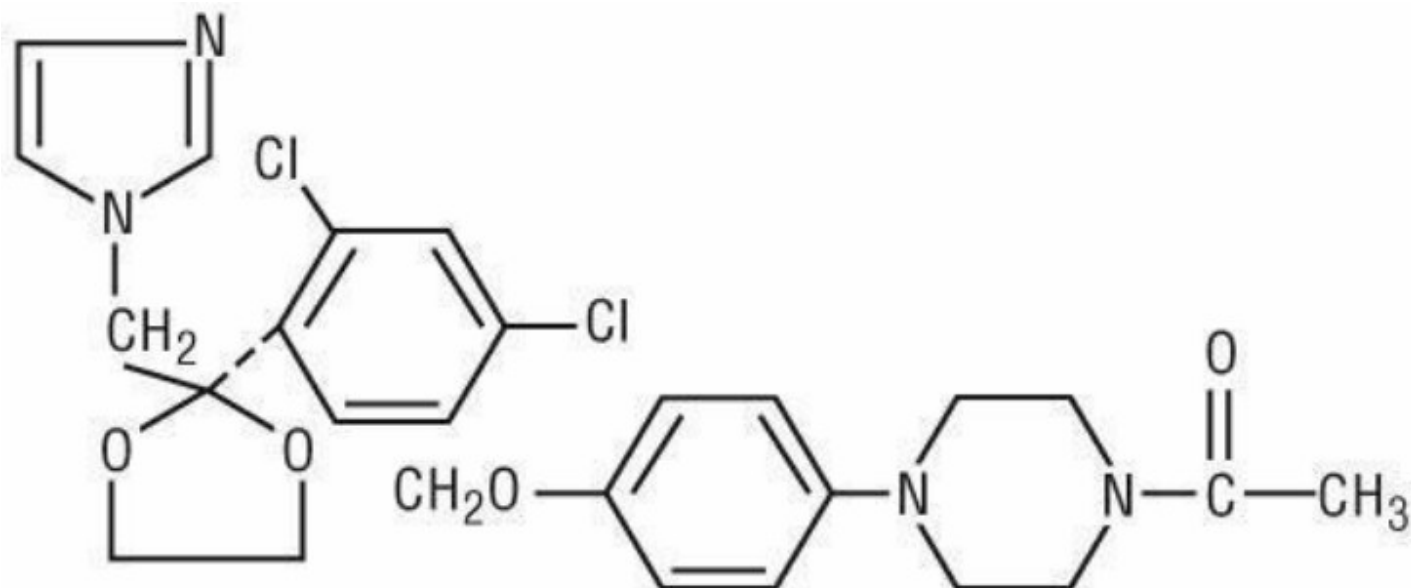
Coadministration of terfenadine with ketoconazole tablets is contraindicated. Rare cases of serious cardiovascular adverse events, including death, ventricular tachycardia and torsades de pointes have been observed in patients taking ketoconazole tablets concomitantly with terfenadine, due to increased terfenadine concentrations induced by ketoconazole tablets. See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** sections.

Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS** sections.

Coadministration of cisapride with ketoconazole is contraindicated. Serious cardiovascular adverse events including ventricular tachycardia, ventricular fibrillation and torsades de pointes have occurred in patients taking ketoconazole concomitantly with cisapride. See
CONTRAINDICATIONS, **WARNINGS**, and **PRECAUTIONS** sections.

DESCRIPTION

Ketoconazole is a synthetic broad-spectrum antifungal agent. Each tablet, for oral administration, contains 200 mg ketoconazole base. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and povidone. Ketoconazole is (\pm)cis-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine and has the following structural formula:



$C_{26}H_{28}Cl_2N_4O_4$ M.W. 531.44

Ketoconazole is a white to slightly beige, odorless powder that is soluble in acids.

CLINICAL PHARMACOLOGY

Mean peak plasma levels of approximately 3.5 mcg/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, ketoconazole 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 cerebral-spinal fluid. Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption.

Ketoconazole tablets are active against clinical infections with *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Phialophora* spp. Ketoconazole tablets are also active against *Trichophyton* spp., *Epidermophyton* spp., and *Microsporum* spp. Ketoconazole is also active *in vitro* against a variety of fungi and yeast. In animal models, activity has been demonstrated against *Candida* spp., *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Malassezia furfur*, *Coccidioides immitis*, and *Cryptococcus neoformans*.

Mode Of Action

In vitro studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes.

INDICATIONS AND USAGE

Ketoconazole tablets are indicated for the treatment of the following systemic fungal infections: candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. Ketoconazole tablets should not be used for fungal meningitis because it penetrates poorly into the cerebral-spinal fluid.

Ketoconazole tablets are also indicated for the treatment of patients with severe recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin, or who are unable to take griseofulvin.

CONTRAINDICATIONS

Coadministration of terfenadine or astemizole with ketoconazole tablets is contraindicated. (See **BOX WARNING, WARNINGS, and PRECAUTIONS** sections.)

Concomitant administration of ketoconazole tablets with cisapride is contraindicated. (See **BOX WARNINGS, WARNINGS and PRECAUTIONS** sections.)

Concomitant administration of ketoconazole tablets with oral triazolam is contraindicated. (See **PRECAUTIONS** section.)

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

WARNINGS

Hepatotoxicity, primarily of the hepatocellular type, has been associated with the use of ketoconazole tablets, including rare fatalities. The reported incidence of hepatotoxicity has been about 1:10,000 exposed patients, but this probably represents some degree of under-reporting, as is the case for most reported adverse reactions to drugs. The median duration of ketoconazole tablet therapy in patients who developed symptomatic hepatotoxicity was about 28 days, although the range extended to as low as 3 days. The hepatic injury has usually, but not always, been reversible upon discontinuation of ketoconazole tablet treatment. Several cases of hepatitis have been reported in children.

Prompt recognition of liver injury is essential. Liver function tests (such as SGGT, alkaline phosphatase, SGPT, SGOT and bilirubin) should be measured before starting treatment and at frequent intervals during treatment. Patients receiving ketoconazole tablets concurrently with other potentially hepatotoxic drugs should be carefully monitored, particularly those patients requiring prolonged therapy or those who have had a history of liver disease.

Most of the reported cases of hepatic toxicity have to date been in patients treated for onychomycosis. Of 180 patients worldwide developing idiosyncratic liver dysfunction during ketoconazole tablet therapy, 61.3% had onychomycosis and 16.8% had chronic recalcitrant dermatophytoses.

Transient minor elevations in liver enzymes have occurred during treatment with ketoconazole tablets. The drug should be discontinued if these persist, if the abnormalities worsen, or if the abnormalities become accompanied by symptoms of possible liver injury.

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

Coadministration of ketoconazole tablets and terfenadine has led to elevated plasma concentrations of terfenadine which may prolong QT intervals, sometimes resulting in life-threatening cardiac dysrhythmias. Cases of torsades de pointes and other serious ventricular dysrhythmias, in rare cases leading to fatality, have been reported among patients taking terfenadine concurrently with ketoconazole tablets. Coadministration of ketoconazole tablets and terfenadine is contraindicated.

Coadministration of astemizole with ketoconazole tablets is contraindicated. (See **BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS** sections.)

Concomitant administration of ketoconazole tablets with cisapride is contraindicated because it has resulted in markedly elevated cisapride plasma concentrations and prolonged QT interval, and has rarely been associated with ventricular arrhythmias and torsades de pointes. (See **BOXED WARNING, CONTRAINDICATIONS and PRECAUTIONS** sections.)

In European clinical trials 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 in these patients with serious underlying disease. However, high doses of ketoconazole tablets are known to suppress adrenal corticosteroid secretion.

In female rats treated three to six months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no-effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanism responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

PRECAUTIONS

General

Ketoconazole tablets have been demonstrated to lower serum testosterone. Once therapy with ketoconazole 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. Ketoconazole tablets also decrease ACTH induced corticosteroid serum levels at similar high doses. The recommended dose of 200 mg to 400 mg daily should be followed closely.

In four subjects with drug-induced achlorhydria, a marked reduction in ketoconazole absorption was observed. Ketoconazole tablets require acidity for dissolution. If concomitant antacids, anticholinergics, and H₂-blockers are needed, they should be given at least two hours after administration of ketoconazole tablets. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 mL aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a drinking straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

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, jaundice, dark urine or pale stools (see WARNINGS section).

Drug Interactions

Ketoconazole is a potent inhibitor of the cytochrome P450 3A4 enzyme system. Coadministration of ketoconazole tablets and drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse effects. Therefore, unless otherwise specified, appropriate dosage adjustments may be necessary. The following drug interactions have been identified involving ketoconazole tablets and other drugs metabolized by the cytochrome P450 enzyme system.

Ketoconazole tablets inhibit the metabolism of terfenadine, resulting in an increased plasma concentration of terfenadine and a delay in the elimination of its acid metabolite. The increased plasma concentration of terfenadine or its metabolite may result in prolonged QT intervals. (See **BOX WARNING, CONTRAINDICATIONS, and WARNINGS** sections.)

Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. (See **BOX WARNING, CONTRAINDICATIONS, and WARNINGS** sections.)

Human pharmacokinetics data indicate that oral ketoconazole potently inhibits the metabolism of

cisapride resulting in a mean eight-fold increase in AUC of cisapride. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. Therefore concomitant administration of ketoconazole tablets with cisapride is contraindicated. (See **BOX WARNING**, **CONTRAINDICATIONS** and **WARNINGS** sections.)

Ketoconazole tablets may alter the metabolism of cyclosporine, tacrolimus, and methylprednisolone, resulting in elevated plasma concentrations of the latter drugs. Dosage adjustment may be required if cyclosporine, tacrolimus, or methylprednisolone are given concomitantly with ketoconazole tablets.

Coadministration of ketoconazole tablets with midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. These agents should not be used in patients treated with ketoconazole tablets. If midazolam is administered parenterally, special precaution is required since the sedative effect may be prolonged.

Rare cases of elevated plasma concentrations of digoxin have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor digoxin concentrations in patients receiving ketoconazole.

When taken orally, imidazole compounds like ketoconazole may enhance the anticoagulant effect of coumarin-like drugs. In simultaneous treatment with imidazole drugs and coumarin drugs, the anticoagulant effect should be carefully titrated and monitored.

Because severe hypoglycemia has been reported in patients concomitantly receiving oral miconazole (an imidazole) and oral hypoglycemic agents, such a potential interaction involving the latter agents when used concomitantly with ketoconazole tablets (an imidazole) can not be ruled out.

Concomitant administration of ketoconazole tablets with phenytoin may alter the metabolism of one or both of the drugs. It is suggested to monitor both ketoconazole and phenytoin.

Concomitant administration of rifampin with ketoconazole tablets reduces the blood levels of the latter. INH (Isoniazid) is also reported to affect ketoconazole concentrations adversely. These drugs should not be given concomitantly.

After the coadministration of 200 mg oral ketoconazole twice daily and one 20 mg dose of loratadine to 11 subjects, the AUC and C_{max} of loratadine averaged 302% (± 142 S.D.) and 251% (± 68 S.D.), respectively, of those obtained after co-treatment with placebo. The AUC and C_{max} of descarboethoxyloratadine, an active metabolite, averaged 155% (± 27 S.D.) and 141% (± 35 S.D.), respectively. However, no related changes were noted in the QT_c on ECG taken at 2, 6, and 24 hours after the coadministration. Also, there were no clinically significant differences in adverse events when loratadine was administered with or without ketoconazole.

Rare cases of disulfiram-like reaction to alcohol have been reported. These experiences have been characterized by flushing, rash, peripheral edema, nausea, and headache. Symptoms resolved within a few hours.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The *Ames Salmonella* microsomal activator assay was also negative. A long term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity.

Pregnancy

Teratogenic effects

Pregnancy Category C

Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in

the diet at 80 mg/kg/day (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

There are no adequate and well controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Ketoconazole has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation. In addition, dystocia (difficult labor) was noted in rats administered oral ketoconazole during the third trimester of gestation. This occurred when ketoconazole was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of oral ketoconazole during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral LD₅₀ of ketoconazole given by gavage to the female rat is 166 mg/kg whereas in the male rat the oral LD₅₀ is 287 mg/kg.

Nursing Mothers

Since ketoconazole is probably excreted in the milk, mothers who are under treatment should not breast feed.

Pediatric Use

Ketoconazole tablets have not been systematically studied in children of any age, and essentially no information is available on children under 2 years. Ketoconazole should not be used in pediatric patients unless the potential benefit outweighs the risks.

ADVERSE REACTIONS

In rare cases, anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported. However, the most frequent adverse reactions were nausea and/or vomiting in approximately 3%, abdominal pain in 1.2%, pruritus in 1.5%, and the following in less than 1% of the patients: headache, dizziness, somnolence, fever and chills, photophobia, diarrhea, gynecomastia, impotence, thrombocytopenia, leukopenia, hemolytic anemia, and bulging fontanelles. Oligospermia has been reported in investigational studies with the drug at dosages above those currently approved. Oligospermia has not been reported at dosages up to 400 mg daily, however sperm counts have been obtained infrequently in patients treated with these dosages. Most of these reactions were mild and transient and rarely required discontinuation of ketoconazole tablets. In contrast, the rare occurrences of hepatic dysfunction require special attention (see **WARNINGS** section).

In worldwide postmarketing experience with ketoconazole tablets there have been rare reports of alopecia, paresthesia, and signs of increased intracranial pressure including bulging fontanelles and papilledema. Hypertriglyceridemia has also been reported but a causal association with ketoconazole is uncertain.

Neuropsychiatric disturbances, including suicidal tendencies and severe depression, have occurred rarely in patients using ketoconazole tablets.

Ventricular dysrhythmias (prolonged QT intervals) have occurred with the concomitant use of terfenadine with ketoconazole tablets. (See **BOX WARNING, CONTRAINDICATIONS**, and **WARNINGS** sections.)

Data suggest that coadministration of ketoconazole tablets and cisapride can result in prolongation of the QT interval and has rarely been associated with ventricular arrhythmias. (See

CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections.)

OVERDOSAGE

In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

DOSAGE AND ADMINISTRATION

Adults: The recommended starting dose of ketoconazole tablets is a single daily administration of 200 mg (one tablet). In very serious infections or if clinical responsiveness is insufficient within the expected time, the dose of ketoconazole may be increased to 400 mg (two tablets) once daily.

Children: In small numbers of children over 2 years of age, a single daily dose of 3.3 to 6.6 mg/kg has been used. Ketoconazole tablets have not been studied in children under 2 years of age.

There should be laboratory as well as clinical documentation of infection prior to starting ketoconazole therapy. Treatment should be continued until tests indicate that active fungal infection has subsided. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. Minimum treatment for candidiasis is one or two weeks. Patients with chronic mucocutaneous candidiasis usually require maintenance therapy. Minimum treatment for the other indicated systemic mycoses is six months.

Minimum treatment for recalcitrant dermatophyte infections is four weeks in cases involving glabrous skin. Palmar and plantar infections may respond more slowly. Apparent cures may subsequently recur after discontinuation of therapy in some cases.

HOW SUPPLIED

Each ketoconazole tablet, USP contains ketoconazole 200 mg available in bottles of 100 and 500. The tablets are white, round, flat-beveled tablets, debossed "93"- "900" on the scored side, plain on the other side.

Store at controlled room temperature between 20° and 25° C (68° and 77° F) (see USP).

Protect from moisture.

Manufactured By:

TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

Printed in USA

Rev. C 11/2003

PACKAGE LABEL - KETOCONAZOLE 200 MG TABLETS

Packaged and distributed by:

STAT Rx USA

Gainesville, GA 30501

Ketoconazole

200mg

14 Tabs

Generic For: **Nizoral**

NDC 16590-998-14

Prod# 998-14
Lot# SAMPLE

Each Tablet Contains: Ketoconazole 200mg USP

Mfg By: Teva Pharmaceuticals USA
Sellersville, PA 18960
NDC 0093-0900-01

Mfg Lot: 30210322A
Discard After: 11/11
BW 8/18/2011 SAMPLE

RX ONLY-KEEP OUT OF REACH OF CHILDREN

Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.

May Cause: dizziness, lightheadedness, fast or pounding heartbeat, easy bruising or bleeding, unusual weakness, numbness or tingling, feeling of severe depression, confusion or thoughts of hurting yourself, nausea, stomach pain, low fever, loss of appetite, weakness, dark urine, clay-colored stools, jaundice

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KETOCONAZOLE			
ketoconazole tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:16590-998(NDC:0093-0900)
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
KETOCONAZOLE (UNII: R9400W927I) (KETOCONAZOLE - UNII:R9400W927I)		KETOCONAZOLE	200 mg
Inactive Ingredients			
Ingredient Name			Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)			
STARCH, CORN (UNII: O8232NY3SJ)			
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)			
MAGNESIUM STEARATE (UNII: 70097M6I30)			
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)			
POVIDONE (UNII: FZ989GH94E)			
Product Characteristics			
Color	white	Score	2 pieces
Shape	ROUND	Size	10mm
Flavor		Imprint Code	93;900
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:16590-998-14	14 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075273	05/31/2011	

Labeler - STAT RX USA LLC (786036330)**Establishment**

Name	Address	ID/FEI	Business Operations
STAT RX USA LLC		786036330	relabel, repack

Revised: 9/2011

STAT RX USA LLC