

# INFORMATION FOR THE PATIENT

## Pr APO-KETOCONAZOLE

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Ketoconazole Tablets USP

### ACTIONS AND CLINICAL PHARMACOLOGY

*In vitro* studies suggest that the antifungal properties of ketoconazole may be related to its ability to impair the synthesis of ergosterol, a component of fungal and yeast cell membranes. Without the availability of this essential sterol, there are morphological alterations of the fungal and yeast cell membranes manifested as abnormal membranous inclusions between the cell wall and the plasma membrane. The inhibition of ergosterol synthesis has been attributed to interference with the reactions involved in the removal of the 14- $\alpha$ -methyl group of the precursor of ergosterol, lanosterol.

### INDICATIONS AND CLINICAL USE

APO-KETOCONAZOLE (ketoconazole) may be indicated for the treatment of serious or life threatening systemic fungal infections in normal, predisposed or immunocompromised patients where alternate therapy is considered inappropriate or has been unsuccessful: systemic candidiasis, chronic mucocutaneous candidiasis, coccidioidomycosis and paracoccidioidomycosis, histoplasmosis and chromomycosis.

The use of APO-KETOCONAZOLE may also be considered in the treatment of severe, recalcitrant dermatophytoses unresponsive to other forms of therapy.

The type of organism responsible for the infection should be identified; however, therapy may be initiated prior to obtaining these results, when clinically warranted.

**N.B.:** The treatment of fungal infections of the CNS is not recommended; ketoconazole penetrates poorly into the CNS.

### CONTRAINDICATIONS

APO-KETOCONAZOLE (ketoconazole) is contraindicated in patients with known hypersensitivity to the drug, and in patients with hepatic dysfunction. Ketoconazole is contraindicated in women of child-bearing potential unless effective forms of contraception are employed.

Concurrent therapy of ketoconazole tablets together with terfenadine is contraindicated. Ketoconazole may inhibit the metabolism of terfenadine, causing increased plasma levels of terfenadine. Increased plasma levels of terfenadine can result in prolonged QT intervals. Cases of severe cardiovascular events including death, cardiac arrest, torsades de pointes and other ventricular dysrhythmias have been reported in patients taking terfenadine in combination with ketoconazole.

Concurrent therapy of astemizole with oral ketoconazole is contraindicated. 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.

Concomitant administration of oral ketoconazole and cisapride is contraindicated because it has resulted in markedly elevated cisapride plasma concentrations and prolonged QT intervals. This interaction has been rarely associated with ventricular arrhythmia and torsade de pointes.

Oral midazolam and triazolam should not be used by patients treated with ketoconazole tablets. Pharmacokinetic data revealed higher and prolonged midazolam concentrations when oral midazolam was administered concomitantly with oral ketoconazole versus placebo. A more pronounced and prolonged hypnotic effect of midazolam was also observed. Metabolism of both ketoconazole and midazolam by the same cytochrome P450 3A isozyme may explain this interaction. Similar pharmacokinetic and pharmacodynamic effects have been observed with triazolam which is primarily metabolized by the same P450 3A isozyme (see PRECAUTIONS, Drug Interactions).

Pharmacokinetic data indicate that another oral antifungal, itraconazole inhibits the metabolism of HMG-CoA reductase inhibitors such as lovastatin. Co-administration of itraconazole and lovastatin resulted in elevated and prolonged plasma concentrations of lovastatin and its active metabolite, lovastatin acid, which may increase the risk of diffuse myalgia and rhabdomyolysis. Based on the chemical resemblance of itraconazole and ketoconazole, HMG-CoA reductase inhibitors such as lovastatin should not be used during treatment with itraconazole.

### WARNINGS

Cases of idiosyncratic hepatocellular dysfunction have been reported during ketoconazole treatment. It is important to recognize that liver disorders can occur during therapy with APO-KETOCONAZOLE (ketoconazole). The occurrence of liver disorders while on APO-KETOCONAZOLE could be fatal unless properly recognized and managed. Liver function tests such as SGPT, alkaline phosphatase, SGPT, SGOT and bilirubin should be performed before treatment, after 2 weeks and at periodic intervals during treatment (monthly or more frequently) particularly in patients who are expected to be on prolonged therapy (>2 weeks) or who have a history of significant alcohol consumption. The concurrent use of ketoconazole with potentially hepatotoxic drugs should be most carefully monitored, especially in patients who are expected to be on prolonged therapy or who have a history of significant alcohol consumption. Other factors increasing the risk of hepatitis are: women over 50, history of liver disease and known drug intolerance.

A mild transient asymptomatic increase of transaminases or alkaline phosphatase sometimes occurs. This asymptomatic reaction is harmless and does not necessarily require a discontinuation of the therapy but these patients should be monitored. It should be emphasized, however, that the occurrence of symptoms of hepatotoxicity, even with minor elevations of liver enzymes, is an indication for termination of therapy. Deaths have been reported with therapeutic doses of ketoconazole associated with evidence of hepatotoxicity.

Clinical studies in men have shown that single doses of ketoconazole at 200, 400 and 600 mg caused a dose-related decrease in serum testosterone levels, which returned to baseline values 8 to 24 hours later. During chronic administration (12 months) of 200 mg ketoconazole daily, testosterone levels were not significantly suppressed. However, at high doses (1200 mg a day), administration of ketoconazole resulted in a reduction of serum testosterone to the castrate level (24 ng/dL) within 24 hours; this reduction was maintained for the duration of therapy (3-10 months). Oligospermia and azoospermia have been reported at therapeutic doses and above. In 6 healthy females receiving 400 mg once in the late follicular phase and once in the luteal phase, ketoconazole produced a 38% drop in 17- $\beta$ -oestradiol along with a 50% increase in progesterone during the follicular phase as well as a 61% drop in 17- $\beta$ -oestradiol and a 94% increase in progesterone during the luteal phase. Since ketoconazole influences steroid synthesis, the potential for a deleterious effect on puberty and/or fertility must be carefully considered when long-term therapy is contemplated in children.

A single 200 mg oral dose of ketoconazole had no effect on human cortisol levels. After a single dose of 400 or 600 mg, ketoconazole caused a slight non-significant fall in basal cortisol levels from 11.7 to 9.3 and 8.1 mg/dL, respectively. There was a significant blunting of cortisol response to ACTH which was reversible; following a single dose of 400 mg or 600 mg ketoconazole, cortisol levels fell from 25.4 to 15.7 and 13.5 mg/dL, respectively. Chronic (1-34 months) administration of 800 or 1200 mg ketoconazole impaired the ability of the adrenal gland to produce cortisol, although evidence of frank adrenal insufficiency was not observed. In patients predisposed to adrenal insufficiency, in those having marginal adrenal function or during periods of prolonged stress, such as in the intensive care unit, cortisol levels should be monitored regularly. Administration of ketoconazole to males at a dose of 1200 mg/day resulted in a rapid and significant decline in adrenal androgens (androstenedione and dehydroepiandrosterone).

Because the effects of ketoconazole on hormonal pathways are incompletely understood, judicious consideration is recommended before ketoconazole is prescribed on a long-term basis.

Toxicity studies in rats receiving ketoconazole admixed in the diet at doses of 160 mg/kg have indicated that ketoconazole leads to increased bone fragility in females. Therefore, therapeutic doses (400 mg/day) should not be exceeded in patients such as post-menopausal women and elderly patients, susceptible to increased bone fragility. In view of the ability of ketoconazole to interfere with steroid synthesis and vitamin D metabolism, careful consideration should be given prior to the use of ketoconazole in children. During long-term treatment, calcium and phosphorus serum levels should be monitored.

Studies in pregnant rats and in guinea pigs with  $^3\text{H}$ -ketoconazole indicate that ketoconazole crosses the placental barrier. Whereas in the rat, fetal levels of total radioactivity were 6 times lower than those of the placenta, unchanged drug levels were 3.5 times lower in the fetuses. Concentrations of radioactivity in the fetal membrane indicate that ketoconazole is only very slowly eliminated from this membrane. In the pregnant patient, the implications of placental transfer of ketoconazole must be carefully considered.

### PRECAUTIONS

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 would include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stools. Patients who receive ketoconazole concomitantly with potentially hepatotoxic drugs, those who are expected to be on long-term therapy (>2 weeks) as well as those with a history of significant alcohol intake or suspicion of liver disorder should have liver function tests performed before and during the initial days of treatment and at periodic intervals during treatment (monthly or more frequently [see WARNINGS]).

Since ketoconazole influences steroid synthesis, the potential for a deleterious effect on puberty and/or fertility must be carefully considered when long-term therapy is contemplated in children.

Anaphylactic reactions to ketoconazole with severe angioedema have been reported in 2 cases. Cross sensitivity with miconazole may exist and caution is suggested when ketoconazole is administered to patients with a known sensitivity to miconazole.

**Use in Patients with Decreased Gastric Acidity:** Absorption of ketoconazole is impaired when gastric acidity is decreased. In patients also receiving acid neutralizing medicines (eg. aluminum hydroxide) these should be administered at least 2 hours after the intake of APO-KETOCONAZOLE (ketoconazole). In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (eg.  $\text{H}_2$ -antagonists, proton pump inhibitors) it is advisable to administer APO-KETOCONAZOLE with a cola beverage.

**Use in Women of Child-Bearing Age:** In women of child-bearing potential, an effective form of contraception must be used during therapy with ketoconazole.

**Use in Pregnancy:** Ketoconazole has been shown to be teratogenic (syndactyly, oligodactyly, abnormal head and leg formation) in the rat when given at 80 mg/kg administered in the diet. When ketoconazole was given to rats by gavage, evidence of maternal toxicity and embryotoxicity was seen with doses as low as 10 mg/kg. There is no experience with the use of ketoconazole in

pregnant women, but animal experiments in pregnant rats and guinea pigs indicate that ketoconazole crosses the placental barrier and that ketoconazole is only very slowly eliminated from fetal membranes.

Very careful consideration should be given to the implications for both mother and fetus before using APO-KETOCONAZOLE in pregnant patients.

**Use in Nursing Mothers:** Ketoconazole is excreted in the milk. When treatment with APO-KETOCONAZOLE is deemed necessary for the lactating patient, nursing should be stopped before therapy with ketoconazole is initiated.

**Use in Children:** Although ketoconazole has been used in children under 2 years of age, the number of instances is limited and monitoring was not comprehensive. Caution should be exercised when ketoconazole is administered to children and careful hepatic and haematological monitoring is indicated. In view of the ability of ketoconazole to interfere with steroid synthesis and vitamin D metabolism, careful consideration should be given prior to the use of ketoconazole in children. There has been a report of hypoparathyroidism developing in a 6 year old during long-term treatment with ketoconazole. During long-term treatment, calcium and phosphorus serum levels should be monitored.

**Drug Interactions:** Since ketoconazole inhibits certain hepatic P450 enzymes, especially of the CYP 3A family, it may decrease the elimination of coadministered drugs whose metabolism depends on such enzymes. Increased levels of such drugs, when used together with ketoconazole, have been associated with an increase and/or a prolongation of their effects, including side effects. Known examples of potentially serious interactions are:

- Ketoconazole has been reported to increase plasma concentrations of cyclosporine. When ketoconazole and cyclosporine are used concomitantly, the dose requirement for cyclosporine may be substantially reduced in order to achieve appropriate plasma trough levels. Blood levels of cyclosporine should be monitored when the two drugs are given concomitantly.
- Ketoconazole inhibits 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 CONTRAINDICATIONS).
- 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 (see CONTRAINDICATIONS).
- Human pharmacokinetic data indicate that oral ketoconazole potentially inhibits the metabolism of cisapride, increasing its half life and plasma concentration and resulting in a mean eight-fold increase in its AUC. Data suggest that co-administration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG (see CONTRAINDICATIONS).
- After the co-administration 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% ( $\pm 142$  S.D.) and 251% ( $\pm 68$  S.D.), respectively, of those obtained after co-treatment with placebo. The AUC and  $C_{max}$  of descarboethoxyloratadine, an active metabolite, averaged 155% ( $\pm 27$  S.D.) and 141% ( $\pm 35$  S.D.), respectively. However, no related changes were noted in the QT<sub>c</sub> on ECG taken at 2, 6 and 24 hours after the co-administration. Also, there were no clinically significant differences in adverse events when loratadine was administered with or without ketoconazole.
- Pharmacokinetic data suggest that oral ketoconazole may inhibit the metabolism of oral midazolam. In 9 subjects, pretreatment with 400 mg ketoconazole once daily for 4 days resulted in a 15-fold increase in midazolam AUC<sub>0-8h</sub>, an approximate 4-fold increase in  $C_{max}$ , and an approximate 3-fold increase in T<sub>1/2</sub>. Enhanced and prolonged sedative effects were also observed. Similar pharmacokinetic and pharmacodynamic effects have been observed for triazolam which is primarily metabolized by the same P450 3A isozyme. In 9 subjects, pretreatment with 400 mg ketoconazole for 4 days resulted in a 22-fold increase in triazolam AUC<sub>0-8h</sub>, a 3-fold increase in  $C_{max}$ , and a 6-fold increase in T<sub>1/2</sub>. Midazolam and triazolam should not be used by patients treated with ketoconazole (see CONTRAINDICATIONS). If midazolam is administered i.v., special precaution is required since the sedative effect may be prolonged.
- Pharmacokinetic data demonstrate that when co-administered, another oral antifungal, itraconazole inhibits the metabolism of lovastatin, resulting in increased plasma concentrations of lovastatin, and its active metabolite lovastatin acid, and a 20-fold increase in AUC for both compounds. These increased plasma levels potentially elevate the risk of skeletal muscle toxicity such as diffuse myalgia and rhabdomyolysis. Based on the chemical resemblance of itraconazole and ketoconazole, concomitant administration of itraconazole with HMG-CoA reductase inhibitors such as lovastatin is contraindicated (see CONTRAINDICATIONS).
- Ketoconazole may increase the plasma levels of methyl prednisolone and possibly busulphane and tacrolimus. The dosage of such drugs, if co-administered with ketoconazole, should be reduced if necessary.

There have also been reports of decreased insulin needs in diabetic patients treated with ketoconazole. Because of a possible insulin-sparing effect of ketoconazole, insulin requirements should be assessed more frequently when ketoconazole is used concomitantly with insulin.

Since administration of rifampicin and/or enzyme inducers such as isoniazid in conjunction with ketoconazole reduced the blood levels of the latter, these drugs should not be administered concomitantly.

There has been a report of an interaction between ketoconazole and phenytoin in patients receiving concomitant therapy. This interaction is complex and is a result of the opposing actions of both agents on cytochrome P450 enzymes: while ketoconazole tends to inhibit this enzymatic system, phenytoin induces it, resulting in a decrease or an increase of either drug in the plasma.

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

## ADVERSE REACTIONS

Some deaths have occurred during clinical trials with ketoconazole. These may or may not be drug related.

**Gastrointestinal:** Dyspepsia, nausea and/or vomiting (3%), G.I. hemorrhage (<1%), abdominal pain (1.2%), diarrhea (<1%).

**Dermatological:** pruritus (1.5%), alopecia (<1%), purpura (<1%), rash (<1%), dermatitis (<1%).

**Central Nervous System:** headache, dizziness, somnolence, tremors, nervousness, paresthesias (<1% in all cases).

**Endocrinological:** gynecomastia (<1%), dose-dependent decrease in testosterone serum levels, decrease in basal and ACTH-induced cortisol levels, increased serum levels of 17-OH progesterone and decreased urinary levels of 17-ketosteroids, hypoparathyroidism.

**Genitourinary:** oligospermia and azoospermia, impotence, loss of libido, menstrual irregularities.

**Haematological:** thrombocytopenia, eosinophilia, decreased hematocrit, anemia, leukopenia, neutropenia (<1%).

**Hepatic:** idiosyncratic hepatocellular dysfunction (<0.01%; see WARNINGS); transient increases in liver enzymes. Three patients have died in hepatic coma; two when ketoconazole therapy was continued despite icteric symptoms, and the third despite discontinuation of therapy.

**Miscellaneous:** fever and chills, photophobia, idiosyncratic allergic reactions, anaphylactic shock, pronounced dyspnea, arthralgia, sensation of detachment (at 800 mg/day), corneal deposits, cataract enlargement (<1%).

**Post-Marketing:** In rare instances, cases of exanthema, urticaria and reversible increased intracranial pressure (eg. papilloedema, bulging fontanelle in infants) have been reported in association with ketoconazole treatment.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of accidental overdose with APO-KETOCONAZOLE (ketoconazole), supportive measures, including gastric lavage (within the first hour) with sodium bicarbonate, may be employed. Activated charcoal may be given if considered appropriate. It has been reported that ketoconazole cannot be removed by hemodialysis.

## DOSAGE AND ADMINISTRATION

When APO-KETOCONAZOLE (ketoconazole) therapy may be indicated, the type of organism responsible for the infection should be identified, although therapy may be initiated prior to obtaining these results, when clinically warranted.

N.B.: Refer to WARNINGS AND PRECAUTIONS

TABLE 1: General guidelines for the duration of ketoconazole treatment in patients with severe or recalcitrant fungal infections.		
Condition	Recommended Treatment <sup>a</sup>	Response Time <sup>a</sup>
<b>Dermal and Cutaneous Mycoses</b>		
Dermatomycosis	4-8 weeks	4 weeks
Hair or scalp mycoses	4-8 weeks	4 weeks
Pityriasis versicolor	3-6 weeks	3 weeks
Oral thrush	1-2 weeks	1 week
Chronic mucocutaneous candidiasis	6-12 months	4 months
Onychomycosis	6-12 months	3 months
<b>Deep Mycoses<sup>c</sup></b>		
Systemic candidiasis	2-4 weeks	4 weeks
Paracoccidioidomycosis	2-4 months	2 months
Coccidioidomycosis	>6 months	6 months

Histoplasmosis	2-4 months	2 months
Chromomycosis	>6 months	3 months

- a) The final decision on length of therapy in individual patients should be based on clinical and mycological response whenever possible.  
b) If no response is seen during this period, dosage can be increased up to the maximum recommended dose.  
c) In deep mycoses treatment should continue for at least 1 week after apparent eradication of the infecting fungus.

**Adults:** APO-KETOCONAZOLE (ketoconazole) should be administered at a dose of 200 mg once a day. Patients who fail to show a response (see Table 1) may have inadequate blood levels (<1 µg/mL) as determined by bioassay and the dose may be increased to 400 mg. Ketoconazole blood levels can also be determined by an HPLC assay.

A maximum daily dose of 400 mg should not be exceeded.

**Children:**

Weighing 20 kg or less: 50 mg once daily  
Weighing 20-40 kg: 100 mg once daily  
Weighing over 40 kg: 200 mg once daily

A maximum daily dose of 100-400 mg should not be exceeded.

Ketoconazole should be taken once daily with a meal. Concomitant administration of agents which inhibit gastric secretion should be avoided since ketoconazole requires adequate gastric acidity for dissolution. In patients also receiving acid neutralizing medicines (eg. aluminum hydroxide), these should be administered at least 2 hours after intake of APO-KETOCONAZOLE. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (eg. H<sub>2</sub>-antagonists, proton pump inhibitors) it is advisable to administer APO-KETOCONAZOLE with a cola beverage.

**PHARMACEUTICAL INFORMATION**

Drug Substance

*Common Name:* Ketoconazole

*Chemical Names:* 1) Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl]-, cis-;  
2) (±)-cis-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine.

*Structural Formula:*

*Molecular Formula:* C<sub>26</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>  
*Molecular Weight:* 531.44

*Description:* Ketoconazole is an almost white to slightly beige coloured powder which is freely soluble in chloroform, methanol and diluted hydrochloric acid; sparingly soluble in 2-propanol and acetone and practically insoluble in water.

*Stability and Storage Recommendations:* Store at room temperature (15°-30°C) in well closed containers.

**AVAILABILITY OF DOSAGE FORMS**

APO-KETOCONAZOLE (ketoconazole) 200 mg tablets are round, white to slightly grey, flat-faced, bevelled-edged tablets engraved 'AP0-200' above the partial bisect on one side, plain on the other. Available in bottles of 100, 250, 500 or 1000 tablets and unit dose packages of 100 tablets.

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