PRODUCT MONOGRAPH

[Pr] TEVA–KETOCONAZOLE

(Ketoconazole Tablets USP, 200mg)

Antifungal Agent

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PRODUCT MONOGRAPH

TEVA–KETOCONAZOLE

(Ketoconazole Tablets USP, 200mg)

THERAPEUTIC CLASSIFICATION

Antifungal Agent

ACTION 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-α-methyl group of the precursor of ergosterol, lanosterol.

A comparative, two-way, single-dose bioavailability study was conducted between TEVA–KETOCONAZOLE (ketoconazole) 200 mg tablets and NIZORAL® 200 mg tablets. The pharmacokinetic plasma data calculated for the two formulations are tabulated below:

Table 1: Pharmacokinetic Indices for Ketoconazole

	Geometric mean Arithmetic mean (C.V.)		
	TEVA–KETOCONAZOLE (1 x 200 mg Tablet)	NIZORAL®** (1 x 200 mg Tablet)	Ratio of Geometric Means
AUC_T (ng h/mL)	14045 14721 (36)	14045 15066 (44)	100%
AUC_I (ng h/mL)	14328 15027 (35)	14328 15333 (43)	100%
C_{max} (ng/mL)	3944 4042 (21)	3828 3915 (22)	103%
T_{max}* (h)	1.44 (41)	1.59 (50)	—
$t_{½}$* (h)	1.52 (19)	1.60 (20)	—

* For the T_{max} and $t_{½}$ parameters these are the arithmetic means (standard deviation).

** NIZORAL® 200 mg Tablets (Janssen Pharmaceutica Inc., Canada)

INDICATIONS

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.

Its use 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.

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

CONTRAINDICATIONS

TEVA–KETOCONAZOLE (ketoconazole) is contraindicated in patients with known hypersensitivity to the drug and in patients with hepatic dysfunction.

TEVA–KETOCONAZOLE is contraindicated in women of childbearing potential unless effective forms of contraception are employed.

Concurrent therapy of ketoconazole tablets together with terfenadine (which is no longer available on the Canadian market) 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 (which is no longer available on the Canadian market) 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 (which is no longer available on the Canadian market) 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 torsades 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).

Pharmacokinetics 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 elevation and prolonged plasma concentrations of lovasatatin 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 ketoconazole.

WARNINGS

Serious Warnings and Precautions

Oral ketoconazole is associated with hepatic toxicity, including cases with fatal outcomes. Patients receiving this drug should be informed by the health care provider of this risk, and should be closely monitored (**see WARNINGS and PRECAUTIONS sections)**

Liver Toxicity:

Ketoconazole tablets are indicated for the treatment of serious or life threatening systemic fungal infections and should not be considered for mild to moderate infections.

Ketoconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. Hepatotoxicity and death have also been reported to occur at recommended doses and with treatment courses of longer than 10 days.

Liver function must be monitored in all patients who are receiving ketoconazole tablets. Tests should be done before starting treatment, at week 2 and week 4 of treatment, and then continued monthly. Treatment should be stopped if any liver parameters are elevated above 3 times the normal limit.

Transient minor elevations in liver enzymes have occurred during treatment with ketoconazole tablets. The drug should be discontinued if liver enzyme abnormalities persist, if the enzyme abnormalities worsen, or if the abnormalities are associated with symptoms of hepatotoxicity.

If clinical signs or symptoms develop that are consistent with liver disease, such as anorexia, nausea, vomiting, jaundice, fatigue, abdominal pain, dark urine, or pale stools, treatment should be discontinued and liver function testing performed.

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.

Hormonal and Metabolic Effects:

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 to 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-β-estradiol along with a 50% increase in progesterone during the follicular phase as well as a 61% drop in 17-β-estradiol 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 μg/dL respectively. There was a significant blunting of cortisol response to ACTH which was reversible; following a single dose of 400 or 600 mg ketoconazole, cortisol levels fell from 25.4 to 15.7 and 13.5 μg/dL respectively. Chronic (1 to 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}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 (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. 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 neutralising medicines (e.g. aluminum hydroxide) these should be administered at least 2 hours after the intake of TEVA–KETOCONAZOLE (ketoconazole). In patients with achorhydria such as certain AIDS patients and patients on acid secretion suppressors (e.g. H_2-antagonists, proton pump inhibitors) it is advisable to administer TEVA–KETOCONAZOLE with a cola beverage.

Use in Women of Childbearing Age: In women of childbearing 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 use in pregnant patients.

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

Use in Children: The use of ketoconazole tablets has not been systematically studied in children of any age, and essentially no information is available in children under 2 years. Ketoconazole should not be used in pediatric patients unless the potential benefit outweighs the potential risks (See WARNINGS). Caution should be exercised when ketoconazole is administered to children and careful hepatic and hematological 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 therapy with ketoconazole. During long-term treatment, calcium and phosphorus serum levels should be monitored.

Drug Interactions:

Overview:

Ketoconazole is an inhibitor of CYP3A4. Therefore, the following drug interactions may occur (see Table 2 below):

1. Ketoconazole may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with ketoconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant ketoconazole therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, depending on the dose and duration of treatment, ketoconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibitors). This is particularly important when initiating therapy with drugs whose metabolism is affected by ketoconazole.

2. Inducers of CYP3A4 may decrease the plasma concentrations of ketoconazole. Ketoconazole may not be effective in patients concomitantly taking ketoconazole and one of these drugs. Therefore, administration of these drugs with ketoconazole is not recommended.
3. Other inhibitors of CYP3A4 may increase the plasma concentrations of ketoconazole. Patients who must take ketoconazole concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of ketoconazole.

Drug-Drug Interactions:

Table 2: Selected drugs that are predicted to alter the plasma concentration of ketoconazole or have their plasma concentration altered by ketoconazole [1]

Drug plasma concentration increased by ketoconazole	
Antiarrhythmics	digoxin, dofetilide, quinidine, disopyramide
Anticonvulsants	carbamazepine
Antihistamines	terfenadine [2,3], astemizole [2,3]
Antimycobacterials	rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide
Benzodiazepines	alprazolam, diazepam, midazolam[2], triazolam[2]
Calcium Channel Blockers	dihydropyridines (including nisoldipine), verapamil
Ergot Alkaloids	dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)
Gastrointestinal Motility Agents	cisapride [2,3]
Glucocorticosteroids	budesonide, dexamethasone, methylprednisolone, fluticasone
HMG-CoA Reductase Inhibitors	atorvastatin, cerivastatin, lovastatin[2], simvastatin[2]
5-HT_1 Receptor Agonists	eletriptan
Immunosuppressants	cyclosporine, tacrolimus, sirolimus
Oral Hypoglycemics	oral hypoglycemics (i.e. repaglinide)
Protease Inhibitors	indinavir, ritonavir, saquinavir
Oral Anticoagulants	warfarin
Other	alfentanil, buspirone, trimetrexate, trazodone, fentanyl, levacetylmethadol (levomethadyl), halofantrine, cilostazol, methadone

Decrease plasma concentration of ketoconazole	
Anticonvulsants	carbamazepine, phenobarbital, phenytoin
Antimycobacterials	isoniazid, rifabutin, rifampin
Gastric Acid Suppressors/Neutralizers	antacids, H_2-receptor antagonists, proton pump inhibitors
Non-nucleoside Reverse Transcriptase Inhibitors	nevirapine
Increase plasma concentration of ketoconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, lopinavir/ritonavir, ritonavir

[1]This list is not all-inclusive.
[2]Contraindicated with ketoconazole (see **CONTRAINDICATIONS** and below)
[3]Not available in Canada

General:

Ketoconazole inhibits the metabolism of terfenadine (which is no longer available on the Canadian market), 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 (which is no longer available on the Canadian market), 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 potently inhibits the metabolism of cisapride (which is no longer available on the Canadian market), increasing its half-life and plasma concentration and resulting in a mean eight-fold increase in its AUC. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG (see CONTRAINDICATIONS).

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 Cmax

of descarboethoxyloratadine, an active metabolite, averaged 155% (±27 S.D.) and 141% (±35 S.D.), respectively. However, no related changes were noted in the QTc 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.

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 $AUC_{0-\infty}$, an approximate 4-fold increase in C_{max}, and an approximate 3-fold increase in $t_{½}$. 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 $AUC_{0-\infty}$, a 3-fold increase in C_{max} and a 6-fold increase in $t_{½}$. 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.

There has been a report of potentiation of the action of warfarin by ketoconazole. In patients, the possibility of a sharp drop in the prothrombin level during concomitant administration of ketoconazole with antivitamin-K type oral anticoagulants should be considered and more careful monitoring of anticoagulant effect is necessary, with an appropriate adjustment of the warfarin dose.

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.

There has been a report of an interaction between ketoconazole and phenytoin in a patient 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.

Pharmacokinetics 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 elevation 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 ketoconazole.

ADVERSE EFFECTS

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

Gastrointestinal: dyspepsia, nausea and/or vomiting (3%), GI hemorrhage (<1%), abdominal pain (1.2%), diarrhea (<1%).

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

CNS: headache, dizziness, somnolence, tremors, nervousness, paresthesias, rare cases of increased intracranial pressure (<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.

Hematological: 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%).

SYMPTOMS AND TREATMENT OF OVERDOSE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of accidental overdosage with 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

Adults: TEVA-KETOCONAZOLE (ketoconazole) should be administered at a dose of 200 mg once a day. Patients who fail to show a response (see Table 3) 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.

General guidelines for the duration of oral ketoconazole treatment should be consistent with the indications of severe or recalcitrant fungal infections. Due to its risk of hepatotoxicity, ketoconazole should not be considered for mild or moderate infections. There should be laboratory as well as clinical documentation of infection prior to starting ketoconazole therapy.

Table 3: Condition and Duration of Treatment

Condition	Recommended Treatment [a]	Response Time [b]
Severe, Recalcitrant Dermatophytoses		
Dermatomycoses	4–6 wks	4 wks
Scalp mycoses	4–8 wks	4 wks
Chronic mucocutaneous candidiasis	6–12 mos	4 mos
Onychomycosis	6–12 mos	3 mos
Deep Mycoses[c]		
Systemic candidiasis	2–4 wks	4 wks
Paracoccidioidomycosis	2–4 mos	2 mos
Coccidioidomycosis	>6 mos	6 mos
Histoplasmosis	2–4 mos	2 mos
Chromomycosis	>6 mos	3 mos

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.

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 neutralising medicines (e.g. aluminum hydroxide) these should be administered at least 2 hours after the intake of TEVA–KETOCONAZOLE. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (e.g. H_2-antagonists, proton pump inhibitors) it is advisable to administer TEVA–KETOCONAZOLE with a cola beverage.

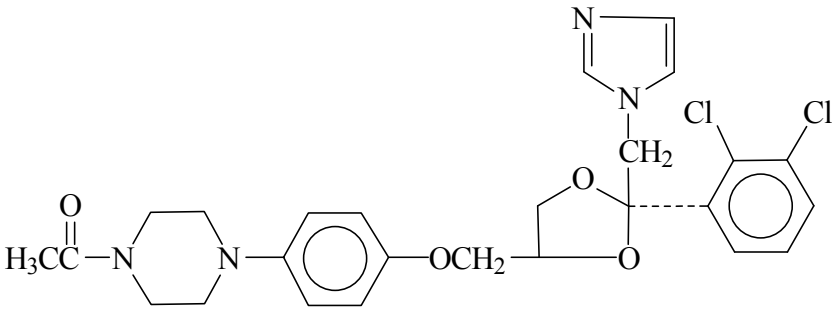
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Ketoconazole

Chemical Name: (±) cis–1–acetyl–4–[p–[[2–(2,4–dichlorophenyl)– 2–imidazol–1–ylmethyl) –1,3–dioxolan –4–yl] methoxy]phenyl]piperazine.

Structural Formula:



Molecular Formula: $C_{26}H_{28}Cl_2N_4O_4$ Molecular Weight: 531.44

Description: Ketoconazole is a white to creamy white coloured crystalline powder which is freely soluble in chloroform, methanol and diluted hydrochloric acid; sparingly soluble in 2-propanol and acetone and practically insoluble in water.

Composition: TEVA–KETOCONAZOLE (ketoconazole) contains: pregelatinized starch, sodium starch glycolate, lactose, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C - 30°C. Unit dose strips should be stored between 15°C - 25°C and protected from high humidity.

AVAILABILITY OF DOSAGE FORMS

TEVA-KETOCONAZOLE (ketoconazole) tablets are off white, scored tablets embossed with '**200'** on one side and 'N/N**'** with vertical bisect on the other side, containing 200 mg of ketoconazole. Available in bottles of 100, 500 and 1000 and in unit dose strips of 100.

MICROBIOLOGY

In Vitro

In yeast and fungal cells, ergosterol is the main sterol regulating membrane permeability. Ketoconazole inhibits the biosynthesis of ergosterol and affects the synthesis of triglycerides and phospholipids.

Morphologically, ketoconazole-induced alterations are characterized by the presence of abnormal membranous inclusions between the cell wall and plasma membrane. Changes in oxidative and peroxidative enzyme activities, leading to an intracellular buildup of toxic concentrations of hydrogen peroxide, may contribute to the observed deterioration of subcellular organelles and to cell necrosis. In *Candida albicans*, ketoconazole inhibits the transformation of blastospores into the invasive mycelial form. This inhibition facilitates the task of host defense cells (phagocytosis) and may be the principal factor leading to the clearance of infection. Ketoconazole is fungistatic at low concentrations (0.05 mcg/mL) and fungicidal at very high concentrations (>50 mcg/mL) against *C. albicans*.

The minimum inhibitory concentration of ketoconazole against a variety of yeasts and fungi can be observed in the following table:

Table 4: Minimum inhibitory concentration of ketoconazole against a variety of yeasts and fungi

Organism	No. of Strains Tested	Range of Minimal Inhibitory Conc. (mcg/mL)
Dermatophytes		
Microsporum canis	24	0.1 – 64
Microsporum audouini	4	2 – 64
Microsporum gypseum	9	0.1 – 64
Microsporum cookie	1	1
Trichophyton mentagrophytes	24	0.1 – 20
Trichophyton rubrum	75	10^{-5} – 128
Trichophyton labelloid	1	1
Trichophyton schoenleini	1	1
Trichophyton tonsurans	35	0.25 – 16
Epidermophyton floccosum	23	0.1 -8
Trichophyton verrucosum	8	0.1 -1
Trichophyton violaceum	3	1
Yeasts		
Candida albicans	472	0.02–80
Candida tropicalis	45	0.1–80
Candida pseudotropicalis	2	25–50
Candida guilliermondii	4	0.4–50
Candida krusei	14	0.2–31
Candida parapsilosis	18	0.2–64
Candida stellatoidea	1	0.8
Cryptococcus neoformans	39	0.1–32
Torulopsis glabrata	124	0.8–64
Rhodotorula mucilanginosa	1	0.1
Trichosporon cutaneum	1	0.1
Dimorphic Fungi		
Blastomyces dermatitidis	26	0.1–2
Coccidioides immitis	30	0.1–0.8
Histoplasma capsulatum	26	0.1–0.5
Paracoccidioides brasiliensis	5	0.002–0.1
Eumycetes		
Acremonium falciforme	1	10
Madurella grisea	1	0.1
Madurella mycetomi	1	0.1
Petriellidium boydii	23	0.1–4
Actinomycetales		
Actinomadura madurae	2	10–25
Nocardia asteroides	1	1
Nocardia brasiliensis	2	10–32
Nocardia cavea	1	1
Streptomyces sp.	1	10

Table 4: Minimum inhibitory concentration of ketoconazole against a variety of yeasts and fungi (continued)

Organism	No. of Strains Tested	Range of Minimal Inhibitory Conc. (mcg/mL)
Phycomycetes		
Absidia corymbifera	1	1
Rhizopus nigricans	1	100
Saprolegnia sp.	1	1
Various Fungi		
Aspergillus flavus	2	1
Aspergillus fumigatus	55	1–100
Aspergillus glaucus	1	1
Aspergillus nidulans	1	1
Aspergillus niger	6	1–16
Aspergillus terreus	3	1
Aspergillus sp.	3	5.5–100
Geotrichum candidum	1	1
Piedraia hortai	1	0.1
Sporothrix schenckii	23	0.1–16
Dematiacious Fungi[a]	29	0.1–64

[a] Cladosporium sp., Fonsecaea sp. and Phialophora sp.

The development of resistance to ketoconazole over a one year treatment period has been reported in 2 patients treated for mucocutaneous candidiasis, however, the *in vitro* sensitivities pre-treatment and after treatment were determined by different techniques.

In vivo

Ketoconazole has been studied in a variety of experimental yeast, dermatophyte and dimorphic fungus infections in animals. Therapeutic efficacy has been demonstrated against *Candida albicans* in rats, mice, guinea pigs, rabbits, turkeys and chickens, against *Trichophyton mentagrophytes* and *Microsporum canis* in guinea pigs and against *Coccidioides immitus. Blastomyces dermatitidis, Cryptococcus neoformans* and *Histoplasma capsulatum* in mice.

PHARMACOLOGY

Animal Pharmacokinetics

The absorption, plasma levels and elimination of a single oral dose of 10 mg/kg of ^{3}H-ketoconazole has been studied in fasted male Wistar rats, male albino guinea pigs, male New Zealand rabbits and female beagle dogs.

Absorption and elimination may be described by a one-compartment model with first order kinetics. Sex related differences in the hepatic metabolizing system of rats have been demonstrated for ketoconazole. Following a single oral dose of 20 mg/kg ^{3}H-ketoconazole, peak plasma levels of approximately 30-35 μg/mL were attained 15 minutes to 1 hour after dosing in male rats whereas they occurred from 1 to 4 hours after dosing in female rats. Elimination in the alpha-phase was faster in male than female rats ($t_{½}$= 2.4 and 5.4 hours, respectively) and the formation of tritiated water by aromatic hydroxylation was more pronounced in male rats.

The distribution of a single oral dose of 20 mg/kg ^{3}H-ketoconazole was studied in male and female rats. Peak tissue levels of radioactivity were reached one hour after dosing in almost all tissues of the male. Peak times varied somewhat more in females. Tissues were cleared of radioactivity with a half-life similar to that observed in plasma for both males and females, meaning that elimination from tissues was initially faster in males than in females.

Placental transfer of ketoconazole has been assessed by means of whole body autoradiography and quantified by liquid scintillation counting and gas chromatography in the rat.

The metabolism and excretion of a single oral dose of ^{3}H-ketoconazole has been studied in 5 rats (17.6 mg/kg by gavage) and in 2 female dogs (10 mg/kg in capsule form). Ketoconazole is extensively metabolized into a large number of inactive metabolites (>22).

Table 5: Distribution of a single oral dose in male and female rats

Tissue	Peak Concentrations of NVR or TR* (mcg-equiv./mL or g of wet tissue	
	Female	Male
Harder's Gland	243-36.7	135-43.5
Adrenal Gland	156-14.9	95.5-30.4
Liver	124-14.5	125-13.6
Pituitary Gland *	51.0-9.49	60.5-70.6
Plasma	35.5-4.37	30.6-8.14
Thyroid*	32.0-5.62	18.5-12.8
Kidney	30.2-1.81	29.1-5.09
Bone Marrow*	28.5-9.73	23.7-23.1
Ovary	26.1-4.47	-
Prostate Gland	-	13.7-1.48
Epididymis	-	8.34-1.84
Testis	-	5.31-1.23
Lung	25.7-4.77	20.8-1.74
Submaxillary Gland	25.3-2.15	22.6-6.19
Spleen	22.7-3.72	13.5-2.42
Heart	18.8-4.45	12.5-2.88
Esophagus	18.7-5.98	0.26-0.005
Pancreas	18.0-2.27	16.8-2.50
Thymus	17.1-3.65	36.9-51.3

Animal Pharmacodynamics

In mice and rats given single doses of up to 40 mg/kg ketoconazole, no effects were seen in general behavior screening tests. Ketoconazole does not exhibit antihistamine, antiserotonin or adrenergic activity in *in vitro* models.

At 5 mg/L, ketoconazole induced a slight prolongation of the duration of the action potential and of the effective refractory time in Purkinje fibres and papillary muscle preparations of the dog. The recovery time in Purkinje fibres was also prolonged by ketoconazole. There were no significant effects on the electrophysiological characteristics of guinea pig auricular muscle at this concentration.

Cardiac or haemodynamic effects were not observed in anaesthetized dogs at doses of ketoconazole up to 5 mg/kg I.V.; however, when 5 cumulative doses amounting to 7.37 mg/kg I.V. were followed by a bolus injection of 10 mg/kg, a decrease in the pressure-rate product (heart rate x systolic aortic pressure) was seen which was attributed mainly to a decrease in heart rate. Both systolic and diastolic pulmonary arterial pressure increased slightly which suggest enhanced venous return. These changes were transient and appeared within 2.5 minutes of the injection. In conscious dogs, ketoconazole at a dose of 20 mg/kg p.o. given in capsule form had no effect on ECG, blood pressure or behaviour.

In acute tests in rats, oral administration by gavage of >25 mg/kg ketoconazole concomitantly with 1 mg/kg acenocoumarin significantly increased the anticoagulant effect (Quick Time) of acenocoumarin seen 24 hours after administration. Forty-eight hours following subchronic oral administration of 40 mg/kg/day ketoconazole for 5 days the effect on the action of acenocoumarin (8 mg/kg) is no longer apparent.

In rats dosed orally for 13 weeks with 40 mg/kg/day ketoconazole admixed in the diet, adrenal pathology was characterized by a marked fatty surcharge of the fasciculata and the reticularis zones while the glomerulosa was devoid of fat and thin. The fatty surcharge of the inner zones led to macrophagy with lipofuscin formation and accumulation and eventually to an interstitial fibrotic reaction with infiltration of round cells in the neighborhood of the medulla. These changes were more pronounced in female rats than in male rats. These pathological changes may be correlated with the action of ketoconazole on the major biosynthetic pathways for adrenal steroids.

At concentrations within the therapeutic range, ketoconazole blocks ACTH-induced cortisol secretion in *in vitro* preparations of rat adrenal cells. At similar concentrations ketoconazole

dramatically reduces both basal and human chorionic gonadotropin-stimulated testosterone production in *in vitro* preparations of rat Leydig cells.

Human Pharmacology

Ketoconazole is extensively metabolized into a large number of inactive metabolites following absorption from the gastrointestinal tract. The major identified metabolic pathways are: oxidation and degradation of the imidazole and piperazine rings, oxidative *0*-de-alkylation and aromatic hydroxylation. Sex-related differences in the metabolism of ketoconazole have been seen in the rat.

In vitro studies have demonstrated that plasma protein binding of ketoconazole is about 99%, mainly to the albumin fraction. Only negligible amounts of ketoconazole reach the cerebral spinal fluid. About 13% of an oral dose is excreted in the urine within 4 days, of which 2-4% is unchanged drug. The major route of excretion is through the intestinal tract, 57% of the dose being excreted in the faeces within 4 days with 20-65% of this being unchanged drug.

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 sustained 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).

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-β-oestradiol along with a 50% increase in

progesterone during the follicular phase as well as a 61 % drop in 17-β-oestradiol and a 94% increase in progesterone during the luteal phase.

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 µg/dl respectively. There was a significant blunting of cortisol response to ACTH which was reversible; following a single dose of 400 or 600 mg of ketoconazole, cortisol levels fell from 25.4 to 15.7 and 13.5 µg/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. 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).

TOXICOLOGY

Ketoconazole has been administered by the oral (gavage) and intravenous routes to mice, rats, guinea pigs and dogs.

Toxicity after intravenous administration was manifested by spasms, convulsions and dyspnea in rats, mice and guinea pigs; pre-lethal loss of the righting reflex occurred in mice and guinea pigs, and dogs. Toxicity in dogs was also manifested by licking and convulsions.

After oral administration toxicity was manifested in mice, rats and guinea pigs by sedation, catalepsy, ataxia, tremors, convulsions and pre-lethal loss of the righting reflex at doses >320 mg/kg. In dogs, toxicity was manifested by diarrhea and vomiting at doses >80 mg/kg.

Subacute

Four groups of 10 male and 10 female rats were dosed orally for a period of 13 weeks with 0, 10, 40 and 160 mg/kg/day ketoconazole added to the diet. Haematology was normal in all groups. No deleterious effects on serum analyses were seen in males at 10 and 40 mg/kg. At 160 mg/kg potassium and BUN decreased significantly. In female rats dosed at 10 mg/kg no relevant differences in serum analyses were found between control and treated animals. At 40 and 160 mg/kg serum sodium increased significantly, while BUN and potassium decreased. A decrease in chloride and increase in alkaline phosphatase at 160 mg/kg are also considered to be among the drug and dose-related effects.

In control, low and medium dosed males and females and in the high-dosed males no abnormalities were seen in urinalyses. At 160 mg/kg, female rats had increased excretion of urine and decreased creatinine. In 3 of 10 females, casts were seen at the high dose.

In animals of both sexes dosed with 10 mg/kg and in male rats dosed at 40 mg/kg, ketoconazole had no effect on mortality, behaviour, appearance, food consumption, body weight, gross pathology, organ weight, or histology.

Female rats dosed at 40 mg/kg were not significantly different from undosed female rats with respect to mortality, behaviour, appearance, food consumption or body weight. However, at 40 mg/kg discoloured livers were seen in 5/10 female rats, pale adrenals in 5/10 and slightly larger ovaries in 8/10. Marginal increases were seen in the absolute and relative weight of the liver and ovaries.

Histologically the livers of the female rats dosed at 40 mg/kg appeared normal. In the adrenals the following changes were noted: a glomerulosa zone devoid of fat, and a fatty overload in the fasciculata and reticularis zones. The disturbed aspect of the inner zone was a result of increased

RE framework, swelling of pigment-loaded sinusoidal cells and macrophage activity. A clearer aspect of the interstitial tissue of the ovary was also noted at histology. One female dosed at 40 mg/kg exhibited swelling of the convoluted tubule and/or loop of Henle in the kidney.

At 160 mg/kg, 2 male rats died whereas all females survived. Behaviour and appearance was normal in males whereas swollen eyelids were seen in all high-dosed females with some exhibiting this as early as after 2 months of dosing. Fragile leg bones were noted in 9/10 female rats with 4/10 having broken legs. Total food consumption decreased significantly in both sexes as did total weight gain and terminal body weight. These phenomena appeared during the first week of dosing. Gross pathology also revealed the following changes: discoloured livers 6/10 males, 9/10 females; pale adrenals 1/10 male, 9/10 females; pseudopregnancy 9/10 females.

Relative weight increase of liver and adrenals, and increases in the relative and absolute weights of the testes were noted in high-dosed male rats. Female rats exhibited increased absolute and relative weight of liver and adrenals as well as increase in the relative weight of spleen and kidney. Histology indicated the following drug induced changes: slight centrilobular swelling and/or finely granular or blurred aspect of the cytoplasm of the liver with brown hepatocytic pigmentation; swelling of the distal tubules and/or loops of Henle in the kidney; the uterus was small and exhibited an anoestral aspect, the vaginal epithelium was mucified or thin; the ovary was characterized by an increased amount of interstitial glandular tissue with large clear cells, highly vacuolated corpora lutea and conspicuous follicular cysts which were sometimes atretic and leading to interstitial tissue formation; in both sexes the adrenals were characterized by a thin glomerulosa zone devoid of fat, fatty overload in the fasciculata and especially in the reticularis zones with macrophage activity, RE stimulation and eventually infiltration with round cells. The weakness of the bony tissues seen in the high dosed females was manifested on histological examination by diminished diameter of the tibial bone, and irregularities in the mineralization of

the compact bone; cancellous bone hyperplasia and spontaneous fractures which were the sites of callus formation with marked fibrosis eventually extending far into the neighboring tissues.

Chronic

Rats

Four groups of 20 male and 20 female adult Wistar rats received ketoconazole at oral doses of 0, 5, 20 and 80 mg/kg/day added to the diet for a period of 6 months. No adverse effects were seen at the 5 mg/kg dose. One control male and 2 high-dosed females died during the course of the study. Food consumption and body weight were significantly decreased in high dosed males and mid-dosed and high-dosed females. A significant increase in lymphocytes and decrease in segmented heterophils was seen in the mid-dosed and high-dosed males, as well as a significant decrease in serum potassium in mid and high-dosed females. Urinalyses were normal except for the presence of casts in several high-dosed males (11/20) and females (7/20) and in some of the mid-dosed females (4/20).

Gross pathology was normal except for broken legs in 1/20 mid and 6/20 high-dosed females.

Organ weights were normal except for a significant increase in liver weight seen in high-dosed males and females and a significant increase in the weights of the kidneys and brain in the high-dosed females. Histology showed fatty surcharge of the ovary and adrenals in the mid and high-dosed groups. The ovaries showed a tendency to more vacuolation of the corpora lutea and an increase in lipofuscin.

In the adrenals there was fatty surcharge of the fasciculata and reticularis zones, lipofuscin formation and macrophagy. Finally an interstitial fibrotic reaction was noted near the medulla in rats of both sexes dosed at 80 mg/kg and in mid-dosed females.

The potential for the production of ophthalmologic lesions in the presence of ultraviolet irradiation was assessed in 40 female and 40 male adult Wistar rats dosed orally with 40 and 80 mg ketoconazole/100 g food for 3,6 and 12 months. In both untreated and treated UV irradiated rats, some transient vascularization of the cornea and conjunctivitis were seen. There were no differences between groups in mortality, ophthalmoscopic and slit lamp examinations or in the histological examination of the eyes.

In another study, 4 groups of 20 male and 20 female adult Wistar rats received 0, 5, 20 and 80 mg/kg/day ketoconazole through the diet for 18 months. Mortality tended to increase with increasing doses in both sexes; however, these increases were not statistically different from controls except for female mortality at 80 mg/kg/day (15/20 high-dose vs. 7/20 control group). Body weight gain and final body weight were lower in the mid-dosed females and in both the high-dosed males and females. Marginal increases in haemotocrit and haemoglobin were seen in high-dosed females. Other serum analyses and urinalysis values were considered normal except for a decrease in serum potassium in the high-dosed males. Gross pathology revealed the following changes: brownish aspect of the salivary glands and the abdominal fat in some mid-dosed and several high-dosed animals; swollen adrenals in 3/16 high-dosed males, 4/20 mid-dosed females and 2/20 high dosed females; bone fragility in the legs leading to broken legs (control-l, low-dose-5, medium-2, high-6). At 80 mg/kg/day, relative organ weights in both sexes increased. This correlated with a decrease in final body weight. Absolute organ weights were normal in all groups except for an increase in adrenal weights in both males and females. The following histological changes were noted: increased deposition and accumulation of lipogenic pigment in some parenchymal and lymphoid tissues (heart, tongue, liver, spleen, lymph nodes, adrenals); ovaries of the mid and high-dosed females showed an increased number of old corpora lutea, and an increased deposition of yellowish to brown pigment in the interstitial cells; the adrenals of the low-dosed females and the mid and high-dosed males and females showed an

increased vacuolization of the fasciculata and the reticularis zones and a diminished size of the glomerulosa zone. In the rat, ketoconazole shows an affinity for the liver and adrenal glands of both sexes and for the sex organs of the female. Ketoconazole is associated with significant bone fragility which is more pronounced in female than in male rats.

In the rats from the 6, 12 and 18 month oral diet toxicity studies, radiometry and direct photon absorptiometry were applied to assess the significance of the observed increase in bone fragility. The results indicate a dose-related decrease of cortical bone area which is present in both sexes at 40 and 80 mg/kg and to a lesser extent in females dosed at 20 mg/kg. Bone mineral content per unit of width however was unaffected, demonstrating the absence of osteoporosis. The mechanism for this condition remains unclear - the induction of menopause in female rats could be a contributing factor.

Dogs

Four groups of 3 male and 3 female Beagle dogs received ketoconazole for 12 months at 0, 2.5, 10 and 40 mg/kg/day administered in gelatin capsules. Behaviour was normal in the 0, 2.5 and 10 mg/kg/day groups; however, at 40 mg/kg decreased appetite and sporadic emesis were noted in all animals during the entire study. No drug-related mortality was observed; however, body weight gain was significantly lower in the high-dose group during the entire experimental period.

Heart rate, blood pressure and ECG were normal throughout the experiment. Haematology parameters were unchanged except in the high-dose group, where a marginally low haemoglobin value was noted during the entire dosing period. Urinalyses and serum analyses were normal except in the high-dose group, where a marginal decrease of albumin from week 24 onwards and persistently high alkaline phosphatase and SGPT values during the entire dosing period were noted. Gross pathology was normal in all groups except the high-dose group, where all dogs exhibited dark coloured livers, brownish discoloured pancreas, thymus, adrenals, thyroid, testes, ovaries, lymph nodes and fatty tissue and gray coloured ovaries. In the high-dosed group, the

absolute weight of several organs decreased with an increase of the relative organ weight. Absolute and relative liver weight increased in the high-dose group. Histology revealed deposition and marked accumulation of a granular yellowish pigment in macrophages in various tissues (in the ovaries, in the hepatocytes, in the fasciculata and glomerulosa zones of the adrenals, in the biliary epithelium and in the interstitial tissue and Leydig cells of the testis) in a dose-related fashion at 10 and 40 mg/kg/day. The livers of the 40 mg/kg dosed males were devoid of glycogen. Large vacuolated cells were seen in the fasciculata zone of the adrenals of the high-dosed animals of both sexes. Desquamation and spermatid giant cells were conspicuous in some 40 mg/kg dosed dogs and one dog showed reduced spermatogenic activity. Many macrophages with yellowish pigment were seen in the 40 mg/kg dosed dogs and in 2/3 female dogs dosed at 10 mg/kg.

In another experiment, 3 male and 3 female Beagle dogs were orally dosed with gelatin capsules containing increasing doses of ketoconazole (20, 40, 60 mg/kg/day) for a period of 6 months. One animal (60 mg/kg) died of gastroenteritis and nephritis during week 12. A dose-related body weight loss was seen above 20 mg/kg/day coincident with reduced appetite. There was no effect on the ECG at any dose and serum analyses and haematology were normal during the 20 and 40 mg/kg dosage periods.

At 60 mg/kg/day an increase in SGOT and haptoglobin, a slight decrease of total protein and albumin and a pronounced increase of alkaline phosphatase and SGPT were seen. Decreases of haematocrit, haemoglobin and RBC were seen in most animals during the 60 mg/kg dosage period. Both serum analyses and haematology normalized during the withdrawal period. Gross pathology revealed a small sized thymus (decreased absolute and relative weight) and swollen liver (increased relative and absolute weight) at 60 mg/kg; however, these effects were reversible since they normalized during the withdrawal period. Histology indicated the presence of macrophages loaded with lipofuscin in the gallbladder, liver, ileum, spleen, lymph nodes, testes,

ovaries, adrenals and prostate gland. In the liver, lipo-pigment also accumulated in the hepatocytes. Interstitial parotitis with reduced zymogen storage was seen in one dog. No spermatogenic activity was noted in 2/3 dogs - one having an immature aspect and the other a degenerated germinal epithelium. Lipofuscin loaded Leydig cells were noted in 2/3 dogs. An increase of clear replacement cells and reduced amount of secretion of the prostate was noted in the dogs with no spermatogenic activity.

Three male and 3 female Beagle dogs were dosed orally with gelatin capsules at a dose of 80 mg/kg/day. Four animals died during the second week of the study, one died at 3 weeks and one during the fourth week. Anorexia with progressive weight loss and exhaustion was seen in all animals. All animals had an increased heart rate, severe gastroenteritis and clinical icterus. Haematology demonstrated an increase of segmented heterophils and decrease of lymphocytes and platelets. Alkaline phosphatase, SGPT and haptoglobin showed marked increases with increases of SGOT and bilirubin less pronounced. Total protein, albumin and glucose were decreased. Absolute and relative weight increases of the liver and adrenals and a decreased absolute and relative weight of the thymus were observed at necropsy.

Carcinogenicity

Four groups of 50 male and 50 female albino Swiss mice received doses of 0, 5, 20 and 80 mg/kg/day of ketoconazole administered via the diet for 18 months. There were no significant differences between groups on overall mortality or on the time of death. There were no statistically significant differences between groups in the incidence or type of tumours.

In a small number of dosed male mice (4-6%) decreased size of testes and mammary stimulation were seen at necropsy. An increased incidence of brownish aspect of the salivary glands was also noted in animals of both sexes dosed with 80 mg/kg/day. The most significant finding was a dose-

related increase in pathology of the pancreas (brownish aspect) which was not seen in control animals but occurred in approximately 50% of high-dosed males and females.

In the Wistar rat (200 males, 200 females), oral administration of 0,5, 20 and 80 mg/kg/day of ketoconazole in the diet for 24 months did not affect the mortality rate as compared to controls. At necropsy the following dose-related effects were seen: a brownish aspect of the salivary glands and the abdominal fat in medium and high-dosed animals and broken legs in one high-dosed male, 2 medium-dosed females and 10 high-dosed females. These findings have been identified in the 18 month rat toxicity study. The overall incidence of and type of tumours was not significantly different between treated and control groups, except for high-dosed female rats who had a decrease of the overall tumour rate.

Teratology and Reproductive Studies

Reproductive and teratological studies were performed in the rat and the rabbit.

1. Male and Female Fertility Study

Wistar rats received ketoconazole administered through the diet at doses of 0, 10, 20, 40 and 80 mg/100 g food. Twenty dosed males coupled each with a non-dosed female and 20 non-dosed males coupled each with a dosed female were used per group or, in total, 200 males and 200 females. Animals were sacrificed on the 22nd day of pregnancy and the foetuses were delivered by caesarean section.

In the various groups of non-dosed females, no effects could be observed on body weight, food consumption, pregnancy rate and duration of gestation of the adult females. One female mated with a male dosed at 40 mg, died during the study. No effects were observed on the number of implantations, litter size, weight of pups at delivery, number and distribution of live, dead and resorbed foetuses. No teratogenic effects were seen.

In the various groups of females dosed at 10, 20 and 40 mg/100 g food, no effects could be observed on any of the parameters studied. The incidence and type of abnormalities seen in the litters of animals dosed at 10 and 20 mg/100 g food were similar to those in the litters of control animals (waved ribs and the absence of one or more metatarsal or metacarpal bones). At 40 mg/100 g food, abnormal knee formation and hydrops of the hind quarters also observed. The duration of gestation of the pregnant females in this group was normal, however, embryotoxicity was manifested by a decrease in the number of implantation sites, a decrease in litter size, a decreased weight of pups at delivery and an increased resorption rate.

One female dosed at 80 mg/100 g food died. At 80 mg/100 g food, dosed females showed a lower body weight gain and a lower food intake with a decreased pregnancy rate which are indicative of maternal toxicity. At 80 mg/100 g food, a clear teratogenic effect was observed and included syndactyly, oligodactyly as well as abnormal head and leg formation.

Three groups of 13 female Wistar rats were treated daily with 10, 20 and 40 mg/kg ketoconazole by gavage for 28 days. Twenty-five animals acted as controls. Animals were sacrificed 4 and 24 hours after the last drug administration and plasma was assayed for progesterone and 17-β - oestradiol by radioimmunoassay. No differences were detected between treated and control groups. Since ketoconazole is known to influence human progesterone and 17- β -oestradiol levels, the previous fertility studies in rats may be poor indicators for reproduction in the human.

2. Embryotoxicity and Teratogenicity Study

Four studies were done in Wistar rats and one study in New Zealand White rabbits.

In two rat studies, ketoconazole was administered through the diet from day 6 through day 15 of pregnancy at doses of respectively, 0, 10, 40, and 160 mg/100 g food and at 0, 10, 20, 40, 80 and

160 mg/100 g food. Twenty dosed females were used per dosage group, or, in total, 80 and 120 females for the two studies respectively.

In both studies, the body weight gain of the dosed pregnant rats was normal and comparable between groups, except for a possible slight decrease in food consumption apparent in some groups, i.e. 160 mg/100 g food of the first study, and 40 and 80, but not 160 mg/100 g food of the second study, so that no dose-related effect on food consumption was apparent. No mortalities occurred in any group and pregnancy rate was normal in all groups except for the 160 mg/100 g food dosed groups, where the pregnancy rate decreased by approximately 50%. No embryotoxic effects were seen in the 10, 20, 40 and 80 mg/100 g food dosed groups, whereas at 160 mg/100 g food, litter size and weight of pups at delivery decreased. The number of resorptions increased from <2% in control animals to >17.7% and >30% in the high dosed animals of the two studies. These results indicate a definite embryotoxic effect at the 160 mg/100 g food dose.

In rats of both studies dosed at 10, 20 and 40 mg/100 g food, the type (waved ribs, absence of metacarpal and/or metatarsal bones) and incidence of abnormalities was the same as that seen in the undosed control rats except for one female of the second study dosed at 20 mg/100 g who delivered 2 foetuses showing retarded embryological development. At 80 and 160 mg/100 g food a clear teratogenic effect was seen with >70% of the foetuses in both studies having abnormalities which included oligodactylia or syndactylia as well as the aforementioned abnormalities. Coelosomia was also seen in one foetus at 160 mg/kg

In a third rat study, ketoconazole was administered by gavage from day 6 through 15 of pregnancy at doses of 0, 10, 40 and 160 mg/kg body weight. Twenty dosed females were used per dosage group. This study was designed to compare the effects of administering the test substance through the diet at comparable dose levels. Foetuses were delivered by caesarean section on Day 22 of presumed pregnancy.

At doses of 10 and 40 mg/kg, no evidence of maternal toxicity was observed except for an increase in the number of resorptions at 40 mg/kg from 1.2% (control) to 3.6%. There was a dose-related increase in the incidence of oligodactyly in foetuses delivered from the females of this experiment. At 160 mg/kg, 19 of 20 dosed females died between the 3rd and 6th day of drug administration. No pregnancy occurred in the surviving female.

In a fourth rat study, ketoconazole was administered by gavage from day 6 through 15 of pregnancy, at doses of 0, 2.5, 10 and 40 mg/kg body weight. Twenty dosed females were used per dosage group. This study was designed to determine whether the bone missing in the foetuses of Study 3 were actually missing or not yet ossified. Female rats were allowed to deliver their foetuses normally. The results of this experiment indicate that metacarpal and metatarsal bones were not really missing but were ossified when females were allowed to deliver their foetuses normally. However, the incidence of stillborn foetuses increased from a control value of 0.5% to 32.7% in rats dosed with 40 mg/kg and cannibalization of young occurred in two litters.

In a rabbit study, ketoconazole was administered by gavage from day 6 through 18 of pregnancy at doses of 0, 10, 40 mg/kg body weight. Twenty dosed females were used per dosage group. The rabbits were artificially inseminated and foetuses were delivered by caesarean section on day 28 after the dam was inseminated. Survival rate was 100% for the control and 10 mg/kg groups. Two females dosed at 40 mg/kg died. The number of resorptions was increased significantly in a dose-dependent manner from 8.1% in control animals to 21.2% and 27.2% in animals dosed at 10 and 40 mg/kg, respectively. Bone deformities were seen in foetuses born to both control and treated animals although at 40 mg/kg their incidence was increased. One foetus born to a control animal had exencephaly and one born to the high dosage group was small sized and had coelosomy. In the rabbit, ketoconazole produces evidence of maternal toxicity, embryotoxicity and teratogenicity at a high dose of 40 mg/kg/day.

3. Peri- and Postnatal Study

Two studies were done in Wistar rats. In the first study, ketoconazole was administered through the diet at doses of 0, 10, 40 and 160 mg/100 g food and, in the second study, ketoconazole was given by gavage at doses of 0, 10, 40 and 80 mg/kg body weight.

Ketoconazole was administered from day 16 of pregnancy through a 3 week lactation period. Twenty females per dosage group were used or, in total, 160 females. Again, both studies were designed to compare the effects of the administration of ketoconazole through the diet and by gavage.

When administered through the diet at a dose of 10 mg/100 g food, no effects could be observed on body weight, food consumption, mortality, pregnancy rate and duration of gestation. Also, no effects were observed on litter size, weight of pups at birth and at 3 weeks of age, and survival rate during a 3 week observation period. At 40 mg/100 g food, the only evidence of maternal toxicity was a slight decrease (approximately 12%) of food consumption. At 40 mg/100 g food, there was a 15% reduction in the number of live foetuses and a similar decrease in the survival rate of the pups was seen at 3 weeks indicating that ketoconazole is embryotoxic at 40 mg/100 g food. No abnormalities were recorded in the litters; however, at 40 mg/kg, cannibalism by the mother occurred in 2 litters.

At a dose of 160 mg/kg maternal toxicity was indicated by a 10% mortality, lower weight gain (1/10th of control), lower food consumption (approximately 30% reduction) and a slightly decreased pregnancy rate (20% reduction). Embryotoxicity was indicated by an increase (approximately 10%) in the percentage of stillborn foetuses. This figure is possibly low due to an increase in cannibalization of foetuses (37% of litters). Birth weight was lower and most pups died shortly after birth. Surviving pups showed no weight increase after a 3-week period.

When ketoconazole is administered by gavage to pregnant rats, maternal and embryotoxicity occur in a dose-dependent manner. At 10 mg/kg, the average weight gain of the dams is reduced by 15% although food consumption is minimally affected. At this same dose the percentage of still born foetuses increased to 3.4% as compared to <1% in control animals and mean litter size decreased from 12.4 in controls to 10.4 in rats dosed at 10 mg/kg. At 40 mg/kg and 80 mg/kg, maternal toxicity was manifested by increased mortality (25 and 90%, respectively). Furthermore at 40 mg/kg, 50% of the foetuses were stillborn and the remainder died shortly after birth. At 80 mg/kg, no live foetuses were born.

In animal studies, the toxicity of ketoconazole was manifested at lower doses when ketoconazole was administered by gavage as opposed to being admixed in the diet.

Mutagenicity:

In vitro Studies

No mutagenic activity was observed in the Ames test with S. typhimurium in the presence of metabolic activating enzymes at doses of ketoconazole up to 50 mcg/plate.

In vivo Studies

In the dominant lethal test in male and female mice, no increased incidence of mutations was observed in the offspring of male or female animals after doses of ketoconazole up to 160 mg/kg. In the micronucleus test in male mice, no effect was observed at doses up to 80 mg/kg.

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr TEVA-KETOCONAZOLE
(Ketoconazole Tablets USP)

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-KETOCONAZOLE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-KETOCONAZOLE is one of a group of medicines called antifungals.

TEVA-KETOCONAZOLE is prescribed by your doctor and is used to treat serious and life-threatening infections in the body caused by fungi including yeasts. The most common cause of fungal infection is a yeast called *Candida*.

What it does:
TEVA-KETOCONAZOLE selectively interferes with the normal sterol production in fungi and helps to stop fungal growth.

When it should not be used:
Do not take TEVA-KETOCONAZOLE if you have ever had an allergic reaction to:

- any of the ingredients of TEVA-KETOCONAZOLE (see What the nonmedicinal ingredients are)
- other medicines you have taken to treat a fungal infection.

The symptoms may include itching, reddening of the skin or difficulty in breathing.

Do not take TEVA-KETOCONAZOLE if you are taking any of the following drugs:

- Cisapride* (used as a gastrointestinal motility agent),
- Terfenadine* or astemizole* (antihistamines for allergies),
- Benzodiazepines such as midazolam, triazolam, or similar medicines (used to help you sleep or for anxiety)
- HMG-CoA reductase inhibitors (eg. lovastatin, for lowering cholesterol)
- Do not take TEVA-KETOCONAZOLE if you are a woman of child-bearing potential unless effective forms of contraception are used.

* not marketed in Canada

What the medicinal ingredient is:
ketoconazole

What the nonmedicinal ingredients are:
pregelatinized starch, sodium starch glycolate, lactose, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate.

What dosage forms it comes in:
blets; 200mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Oral ketoconazole is associated with liver (hepatic) toxicity, including cases of death. Your doctor will tell you of the risk and monitor your situation.

BEFORE you use TEVA-KETOCONAZOLE talk to your doctor or pharmacist if you:

- **have liver or kidney problems**
- **are allergic to any other medicines including those used to treat yeast and other fungal infections**
- **have abnormal levels of potassium, calcium or magnesium in your blood**
- are pregnant or are planning to become pregnant.
- are breast-feeding or planning to breast-feed. TEVA-KETOCONAZOLE is excreted in human breast milk. Breast-feeding is not recommended.
- have heart disease such as heart conditions, blood disorders or any other medical conditions.
- are driving and using machines. It should be taken into account that occasionally dizziness or seizures may occur.
- are taking or have taken any other medicines, including medicines obtained without a prescription
- **Use in Children**
  Your doctor will decide whether this medication is suitable for your child.

Your doctor may test your liver function, before and during treatment.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with TEVA-

KETOCONAZOLE include:

- Alfentanil, fentanyl or methadone (used to treat pain)
- Antiarrhythmics (e.g. digoxin, quinidine, disopyramide)
- Antipsychotics (e.g. pimozide)
- Amitriptyline, nortriptyline (used to treat migraine)
- Amphotericin B and Voriconazole (used to treat fungal infections)
- Calcium channel blockers or losartan (for lowering blood pressure)
- Carbamazepine or phenytoin (used to control epilepsy)
- Celecoxib (used to treat some types of arthritis)
- Cimetidine (for heartburn and peptic ulcers)
- Coumarin-Type Anticoagulants (used to thin the blood to prevent blood clots)
- Cyclophosphamide, prednisone or vinca alkaloids (for treating some forms of leukaemia)
- Cyclosporine, sirolimus or tacrolimus (to prevent transplant rejection)
- Ergot alkaloids (e,g. ergotamine, methylergometaine)
- Glucocorticoids (e.g. dexamethasone, fluticasone).
- Halofantrine (to treat malaria)
- Medicines for treating infections (antibiotics) such as azithromycin, erythromycin, rifampin or rifabutin
- Non-steroidal anti-inflammatory drugs (such as acetylsalicylic acid and ibuprofen) that are used to treat pain and fever
- Oral Contraceptives
- Saquinavir or zidovudine, also known as AZT (used in HIV-infected patients)
- Sulfonylureas and other Oral Hypoglycemics (medicines for diabetes)
- Theophylline (used to control asthma)
- Vitamin A (as a trans-retinoid acid used to treat acne)
- Water tablets (diuretics), such as hydrochlorothiazide, (used to treat fluid retention and high blood pressure)

PROPER USE OF THIS MEDICATION

Usual Adult dose:
Take TEVA-KETOCONAZOLE, 200mg or 400mg once a day with a meal as determined by the doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, TEVA-KETOCONAZOLE may cause some side effects.
The most common side effects are:

- Headache,
- Skin rash,
- Abdominal pain,
- Diarrhea,
- Nausea and vomiting

If you develop symptoms of liver problems, such as nausea, vomiting, abdominal pain, dark urine, pale stools or yellowing of the skin or eyes, stop taking TEVA-KETOCONAZOLE immediately and contact your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Exfoliative skin disorders: Severe skin reactions, such as a rash that causes blistering, itching all over the body, reddening of the skin or itchy red spots, swelling of eyelids, face or lips, peeling or lost skin		√	
Hepatic necrosis (death of liver cells which may cause abdominal pain and dark urine, fever, light-colored stool, and jaundice (a yellow appearance to the skin and white portion of the eyes)		√	
Heart conditions: Unstable or irregular heartbeat (e.g. QT prolongation, torsade de pointes)		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and call your**
Allergic Reaction with symptom such as swelling of the face, throat, mouth, extremities, difficulty in breathing, rash or itching			√

This is not a complete list of side effects. For any unexpected effects while taking* TEVA-KETOCONAZOLE, *contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15 and 30°C. Unit dose strip should be stored between 15 and 25°C and protected from high humidity.

Keep this and all medications out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Teva Canada Limited at:
1-800-268-4127 ext. 1255005 (English
1-877-777-9117 (French)
or druginfo@tevacanada.com

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