

SM PHARMACEUTICALS SDN. BHD.

KETOBID (KETOCONAZOLE) TABLET 200 MG

DESCRIPTION:

White, round, biconvex tablet with break line.

COMPOSITION:

Each tablet contains 200 mg Ketoconazole

PHARMACOLOGY (SUMMARY OF PHARMACODYNAMICS AND PHARMACOKINETICS):

PHARMACODYNAMICS

Ketoconazole is a synthetic, broad-spectrum antifungal agent with a fungicidal or fungistatic activity against dermatophytes, yeasts and other pathogenic fungi.

Ketobid Tabs are active against clinical infections with *Blastomyces dermatitis*, *Candida spp.*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Malassezia furfur*, and *Phialophora spp.* Ketobid Tablets are also active against *Trichophyton spp.*, *Epidermophyton spp.*, and *Microsporum spp.*

Ketoconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the membrane therefore alters the permeability of the cell membrane of sensitive fungi.

Ketoconazole has activity against some Gram-positive bacteria.

PHARMACOKINETICS

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

INDICATIONS:

Ketobid Tablet 200mg (ketoconazole) Tablets should be used only when other effective antifungal therapy is not available or tolerated and the potential benefits are considered to outweigh the potential risks.

Ketobid Tablet 200mg (ketoconazole) Tablets are indicated for the treatment of the following systemic fungal infections in patients who have failed or who are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis.

Ketobid Tablet 200mg (ketoconazole) Tablets should not be used for fungal meningitis because it penetrates poorly into the cerebrospinal fluid.

Oral products containing ketoconazole are restricted for hospital use only

CONTRAINDICATIONS:

Coadministration of terfenadine or astemizole with ketoconazole tablets is contraindicated.

Concomitant administration of Ketobid Tablets with cisapride or triazolam, oral midazolam, quinidine, primozide, CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin.

Ketobid is contraindicated in patients who have shown hypersensitivity to the drug. Since ketoconazole has been reported to cause hepatotoxicity it should not be administered to patients with pre-existing liver disease.

In patients with acute or chronic liver disease

SIDE EFFECTS / ADVERSE REACTIONS:

Ketoconazole is very well tolerated. The most frequent adverse reactions were gastrointestinal disturbances, nausea and/or vomiting, abdominal pain and pruritus. In rare instances, headache, dizziness, somnolence, fever and chills, photophobia, diarrhoea, constipation, impotence, menstrual irregularities, thrombocytopenia, leukopenia, haemolytic anaemia, bulging fontanelles, papilledema, exanthema or itching may develop. Other side effects reported with an extremely low incidence are alopecia, parasthesia, urticaria and rash. In a few patients allergic reactions have been reported.

With doses higher than the recommended therapeutic dose of 200 or 400 mg daily, reversible gynecomastia and oligospermia have been observed in rare cases.

During treatment with ketoconazole, hepatitis may rarely develop (as observed in 1/12,000 patients). Such side effect mostly occurs in patients with a history of liver disease or drug allergy and may be reversed when the treatment is discontinued in time.

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

Post-marketing Experience

Hepato-biliary Disorders

Very rare: serious hepatotoxicity, including hepatitis cholestatic, biopsy-confirmed hepatic necrosis, cirrhosis, hepatic failure including cases resulting in transplantation or death (see WARNINGS AND PRECAUTIONS)

PRECAUTIONS / WARNINGS:

It is thus important to make the patient aware of symptoms of liver disease, e.g. abnormal fatigue with fever, dark urine, pale stools or jaundice. An appropriate laboratory examination should thereby be carried out. When this confirms liver disease, the therapy is to be discontinued. It should be noted, however, that in patients with fungal infections, whether they are treated with Ketobid or not, a mild transient asymptomatic increase of transaminases or of alkaline phosphatase sometimes occurs. This asymptomatic reaction is harmless and does not require a discontinuance of the therapy. Patients on chronic therapy should have a regular monitoring (monthly) of liver function test.

Fertility

At the therapeutic dose of 200 mg once daily, a transient decrease in the plasma levels of testosterone can be observed. Testosterone levels normalize within 24 hours after administration of ketoconazole. During long-term therapy at this dose, testosterone levels are usually not significantly different from controls. Ketoconazole has been shown to decrease or abolish serum testosterone concentrations when used in high doses (e.g., 800 mg to 1.6 grams daily).

Achlorhydria

In 4 subjects with drug-induced achlorhydria, a marked reduction in ketoconazole absorption was observed. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 ml aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a drinking straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

Adrenal function and stress

In volunteers at daily doses of 400 mg and more, ketoconazole has been shown to reduce the cortisol response to ACTH stimulation. Therefore, adrenal function should be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc).

Labour

Ketoconazole has also been shown to cause dystocia in rats given doses greater than 10 mg/kg (> 1.25 times the MRHD) during the third trimester.

Paediatric Use:

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

Mutagenesis, Carcinogenesis, Impairment of Fertility:

The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The *Ames Salmonella* microsomal activator assay was also negative. Long-term feeding studies in Swiss Albino mice and in Wistar rats have not shown evidence of oncogenesis.

Fertility was reduced in male rats treated with about 80 mg/kg and in female rats treated with 40 mg/kg.

Because of the risk for serious hepatotoxicity, Ketobid Tablet 200mg should be used only when the potential benefits are considered to outweigh the potential risks, taking into consideration the availability of other effective antifungal therapy. Assess liver function, prior to treatment to rule out acute or chronic liver disease, and monitor at frequent and regular intervals during treatment, and at the first signs or symptoms of possible hepatotoxicity

Hepatotoxicity

Very rare cases of serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Cases have been reported that occurred within the first month of treatment, including some within the first week.

The cumulative dose of the treatment is a risk factor for serious hepatotoxicity. Factors which may increase the risk of hepatitis are prolonged treatment with ketoconazole tablets, females over 50 years of age, previous treatment with griseofulvin, a history of liver disease, known drug intolerance and concurrent use of medication which compromises liver function. A period of one month should be allowed between cessation of griseofulvin treatment and commencement treatment with ketoconazole tablets because of an apparent association between recent griseofulvin therapy and hepatic reactions to ketoconazole tablets.

Monitor liver function in all patients receiving treatment with ketoconazole tablets (see Monitoring of hepatic function).

Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. In these patients, treatment should be stopped immediately and liver function should be conducted.

Monitoring of hepatic function

Monitor liver function in all patients receiving treatment with ketoconazole tablets. Monitor liver function prior to treatment to rule out acute or chronic liver disease (see CONTRAINDICATIONS), after two weeks of treatment and then on a monthly basis and at the first signs or symptoms of possible hepatic toxicity. When the liver function tests indicate liver injury, the treatment should be stopped immediately.

A risk and benefit evaluation should be made before oral ketoconazole is used in cases of non-life threatening diseases requiring long treatment periods.

In patients with elevated liver enzymes, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases, close monitoring of the liver enzymes is necessary

Use In Pregnancy:

Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg / kg / day (10 times the maximum recommended human dose). Ketoconazole has also been shown to be embryotoxic in rats given doses greater than 80 mg/kg during the first trimester. No studies are available on its use in pregnant women. May not

be administered during pregnancy, unless the potential advantage justifies the possible risk for the foetus.

Use in Lactation:

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

Interactions:

Rifampicin, INH (Isoniazid)

Concomitant administration of rifampicin with ketoconazole reduces the blood levels of the latter. INH (Isoniazid) is also reported to affect ketoconazole concentrations adversely. Both drugs should not be administered concomitantly.

Cyclosporin A

Concomitant administration of cyclosporin A with ketoconazole increases the blood levels of cyclosporin A. Blood levels of cyclosporin A should be monitored if the 2 drugs are given concomitantly.

Terfenadine

Ketoconazole tablets inhibit the metabolism of terfenadine, resulting in an increased plasma concentration of terfenadine and a delay in the elimination of its acid metabolite.

The increased plasma concentration of terfenadine or its metabolite may result in prolonged QT intervals.

Cisapride

Human pharmacokinetics data indicate that oral ketoconazole inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride. Data suggest that co-administration of oral ketoconazole tablets with cisapride can result in prolongation of the QT interval on the ECG. Therefore concomitant administration of ketoconazole tablets with cisapride is contraindicated.

Chlordiazepoxide, Cyclosporine, Tacrolimus, Methylprednisolone, Quinidine

Ketoconazole tablets may alter the metabolism of the above drugs resulting in elevated plasma concentrations of the latter drugs. Dosage adjustment may be required if they are given concomitantly with Ketobid Tablets.

Midazolam and Triazolam

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

Anticholinergic agents, antacids, H₂-receptor antagonists, omeprazole, or didanosine sucralfate

Concomitant administration of drugs that reduce stomach acidity, such as the above, may reduce the absorption of ketoconazole. When indicated, such medications should be taken not earlier than 2 hours after administration of ketoconazole.

Indinavir

Concurrent use of ketoconazole with indinavir increases the AUC for indinavir by 68 %; a dose reduction of indinavir to 600 mg every 8 hours is recommended.

Theophylline

Absorption from sustained release oral dosage forms of theophylline may be reduced by ketoconazole.

Digoxin

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

Coumarin-like drugs / Oral anticoagulants

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

Oral Hypoglycemic / Antidiabetic agents

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

Phenytoin

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

Alcohol

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

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION:

Skin, gastrointestinal and systemic infections:

Adults: 200 mg (1 tablet) daily taken with food. When no adequate response is obtained, the dose should be increased to 400 mg (2 tablets) once daily.

Children may be given approximately 3 mg / kg body weight daily, or 50 mg for those aged 2 to 4 years and 100 mg for those aged 5 to 12 years (15-30 kg).

>30 kg: Same as for adults.

This dosage scheme should be continued without any interruption until at least 1 week after all symptoms have disappeared and until all cultures turn out negative.

Usual Duration of Treatment:

Vaginal Candidiasis: 2 tablets for 5 consecutive days; *skin mycoses* induced by *dermatophytes*, approximately 4 weeks; *pityriasis versicolor*, 10 days; *oral and skin mycosis* induced by *Candida*: 2-3 weeks; *hair infections*: 1-2 months; *nail infections*: 6-12 months, also determined by the speed of nail growth, full outgrowth of the affected nail is required; *systemic candidiasis*: 1-2 months; *paracoccidioidomycosis*, *histoplasmosis*, *coccidioidomycosis*: Minimum treatment is 6 months.

Prophylactic Treatment of Immunodeficient Patients: *Adults*: 2 tablets daily.

Children: 4-8 mg/kg.

SYMPTOMS AND TREATMENT FOR OVERDOSE, AND ANTIDOTE(S):

No cases of accidental or deliberate overdose have been reported.

Symptoms

Should be similar to adverse reactions.

Treatment

In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed to prevent further absorption of the drug.

PACKING / PACK SIZES:

Blister pack of 10's, 10 x 10's / Box

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS:

Store in a dry place, below 30°C.

Protect from light.

For oral use. to be taken with food

SHELF LIFE: 3 years

MANUFACTURER AND PRODUCT REGISTRATION HOLDER:

SM PHARMACEUTICALS SDN BHD (218620-M)

Lot 88, Sungai Petani Industrial Estate

08000 Sungai Petani,

Kedah Darul Aman,

Malaysia.

30.07.2026