

DATA SHEET

NAME OF MEDICINE

NIZORAL™ ketoconazole 200 mg tablet

PRESENTATION

White, scored, tablet marked with 'K/200' and 'Janssen' on reverse.

Indications

Because of the risk for serious hepatotoxicity, NIZORAL tablets 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.

NIZORAL tablets are indicated for the treatment of the following mycoses that cannot be treated topically due to the site or extent of the lesions, in patients resistant to, or intolerant of other effective antifungal agents:

- Dermatophytosis
- Pityriasis versicolor
- Malassezia folliculitis
- Chronic mucocutaneous candidosis
- Cutaneous candidosis
- Oropharyngeal and oesophageal candidosis
- Chronic, recurrent vaginal candidosis.

Ketoconazole does not penetrate well in the CNS. Therefore, fungal meningitis should not be treated with oral ketoconazole.

NIZORAL tablets are also indicated for the treatment of the following systemic fungal infections in patients resistant to, or intolerant of other effective antifungal agents:

- Histoplasmosis
- Blastomycosis
- Coccidioidomycosis
- Paracoccidioidomycosis.

DOSAGE AND ADMINISTRATION

Dosage

Adults

The recommended dose of NIZORAL tablets for all indications is one tablet (200 mg) once daily with a meal, with the exception of vaginal candidosis (see below).

If no adequate response is obtained with this dose after a reasonable trial period, the dosage may be increased to two tablets (400 mg) once daily with a meal

For vaginal candidosis, the recommended dose of NIZORAL tablets is two tablets (400 mg) once daily with a meal.

Children

Children weighing more than 30mg: same as that for adults.

Children weighing 15-30kg: half a tablet (100mg) once daily with a meal.

Children weighing less than 15kg: Not recommended.

Duration

Treatment should be continued without interruption until clinical parameters or laboratory tests indicate that the fungal infection has resolved. An inadequate treatment period may lead to recurrence of the active infection.

However, the risk of serious hepatic toxicity increases with longer duration of treatment. Therefore, long duration of treatment should only be given after full consideration of the extent of treatment response and the risks and benefits of continuing treatment. If treatment is continued, liver function should be closely monitored.

Treatment should be stopped immediately and liver function testing should be conducted when signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine occur (see **WARNINGS AND PRECAUTIONS**)

The usual duration of treatment is as follows:

- Dermatophytosis: approximately 4 weeks
- Pityriasis versicolor: 10 days
- Malassezia folliculitis: 4 weeks
- Oral and skin mycosis caused by Candida: 2-3 weeks
- Vaginal candidosis: 5 consecutive days
- Histoplasmosis: 6 weeks
- Hair infections: 1 to 2 months
- Blastomycosis: 6 months
- Coccidioidomycosis: 6 months
- Paracoccidioidomycosis: 6 months.

Administration

NIZORAL tablets should be taken during meals for maximal absorption.

The absorption of oral ketoconazole is impaired when gastric acidity is decreased. Patients who are receiving acid neutralising medicines (e.g. antacids) should take these medicines at least 2 hours after the intake of NIZORAL. In patients with achlorhydria, such as certain AIDS patients and patients on medicines that suppress gastric acid secretion (e.g. H₂-antagonists, proton pump inhibitors), it is advisable to take NIZORAL with an acidic drink such as a cola beverage.

Special populations

Hepatic impairment (see **Contraindications** section).

CONTRAINDICATIONS

NIZORAL tablets are contraindicated in the following situations:

- Patients with a known hypersensitivity to ketoconazole or any of the excipients (see **Further Information** section)
- Patients with a known hypersensitivity to any other imidazole antifungal
- Patients with acute or chronic liver disease

Concomitant administration of NIZORAL tablets with any of the following medicines is contraindicated:

- CYP3A4 substrates: astemizole, bepridil, cisapride, disopyramide, dofetilide, domperidone, halofantrine, levacetylmethadol, (levomethadyl), mizolastine, pimozone, quinidine, sertindole or terfenadine. Increased plasma concentrations of these medicinal products can lead to QT prolongation and rare occurrences of torsades de pointes.
- Oral midazolam or oral triazolam
- CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin or lovastatin
- Ergot Alkaloids such as ergometrine, methylergometrin, ergotamine or dihydroergotamine)
- Nisoldipine
- Eplerenone
- Irinotecan
- Everolimus

WARNINGS AND PRECAUTIONS

WARNING: because of the risk for serious hepatotoxicity, NIZORAL tablets 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 diseases. Liver function should then be monitored at frequent and regular intervals during treatment (for example, after two and four weeks of treatment and then on a monthly basis). Liver function should also be assessed at the first signs or symptoms of possible hepatotoxicity.

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

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 risk of serious hepatic toxicity increases with longer duration of treatment; therefore long duration of treatment should only be given after full consideration of the extent of treatment response and the risks and benefits of continuing treatment.

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 NIZORAL 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 comprises liver function. A period of one month should be allowed between cessation of griseofulvin treatment and commencement treatment with NIZORAL tablets because of an apparent association between recent griseofulvin therapy and hepatic reactions to NIZORAL tablets.

All patients should be counselled at the start of treatment with basic knowledge of the signs and symptoms suggestive of liver toxicity. The patient should be instructed to promptly report to their physician in the event of symptoms such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. In these patients, treatment should be stopped immediately and liver function testing should be conducted.

Monitoring of Hepatic Function

Monitor liver function in all patients receiving treatment with NIZORAL tablets. Liver function should be assessed prior to treatment to rule out acute or chronic liver disease (see **CONTRAINDICATIONS** section), then monitored at frequent and regular intervals during treatment, (for example, after two and four weeks of treatment and then on a monthly basis). Liver function should also be assessed at the first signs or symptoms of possible hepatotoxicity. When the liver function tests indicate liver injury (for example, any liver parameters are elevated above 3 times the normal limit), the treatment should be stopped immediately.

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, with consideration given to monitoring liver function more frequently.

Monitoring of Adrenal Function

NIZORAL tablets have been shown to reduce the cortisol response to ACTH stimulation in healthy volunteers receiving daily doses of 400mg or more. Therefore, adrenal function should be monitored in patients with Addison's disease, adrenal insufficiency or borderline adrenal function and in patients under prolonged periods of stress (e.g. major surgery, intensive care, etc) and in patients on prolonged therapy presenting signs and symptoms suggestive of adrenal insufficiency.

Decreased gastric acidity

Absorption is impaired when the gastric acidity is decreased. Acid neutralising medicines (e.g. aluminium hydroxide) should not be administered for at least 2 hours after the intake of NIZORAL tablets. In patients with achlorhydria, such as certain AIDS patients and patients on acid secretion suppressors (e.g. H₂-antagonists, proton pump inhibitors), it is advisable to administer NIZORAL with a cola beverage.

Drug Interaction Potential

NIZORAL has a potential for clinically important interactions (**see INTERACTIONS**).

Pregnancy and lactation

Use in pregnancy

Category B3.

NIZORAL tablets should not be administered during pregnancy, unless in the judgement of the treating clinician, such use is deemed essential and the expected benefits to the mother outweigh any potential risks to the foetus.

There are no adequate and well controlled studies of the use of oral ketoconazole in pregnant women. However, ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) and embryotoxic in rats given 80mg/kg/day.

Use in lactation

As ketoconazole is excreted in the milk, mothers who are being treated with NIZORAL tablets should not breastfeed.

Effects on ability to drive and use machines

No effects have been observed.

ADVERSE EFFECTS

Clinical Trial Data

The safety of NIZORAL Tablets was evaluated in 4735 subjects in 92 clinical trials where NIZORAL Tablets were administered to treat a fungal infection or to healthy volunteers.

Adverse drug reactions that were reported in $\geq 1\%$ of NIZORAL Tablets-treated subjects are shown in **Table 1**.

Table 1. Adverse Drug Reactions Reported in $\geq 1\%$ of 4735 NIZORAL Tablets-treated Subjects in 92 Clinical Trials

System Organ Class	%
Preferred Term	
Gastrointestinal Disorders	
Abdominal pain	1.2
Diarrhoea	1.8
Nausea	2.5
Hepato-biliary Disorders	
Hepatic function abnormal	1.2
Nervous System Disorders	
Headache	2.4

Additional adverse drug reactions that occurred in $< 1\%$ of NIZORAL Tablets-treated subjects in the clinical datasets are listed in **Table 2**.

Table 2. Adverse Drug Reactions Reported in $< 1\%$ of 4735 NIZORAL Tablets-treated Subjects in 92 Clinical Trials

System Organ Class
Preferred Term
Endocrine Disorders
Gynaecomastia
Eye Disorders
Photophobia
Gastrointestinal Disorders
Abdominal pain upper
Constipation
Dry mouth
Dysgeusia
Dyspepsia
Flatulence
Tongue discolouration
Vomiting
General Disorders and Administration Site Conditions
Asthenia

Chills

Fatigue

Hot flush

Malaise

Oedema peripheral

Pyrexia

Hepato-biliary Disorders

Hepatitis

Jaundice

Immune System Disorders

Anaphylactoid reaction

Investigations

Platelet count decreased

Metabolism and Nutrition Disorders

Alcohol intolerance

Anorexia

Hyperlipidaemia

Increased appetite

Musculoskeletal and Connective Tissue Disorders

Myalgia

Nervous System Disorders

Dizziness

Paraesthesia

Somnolence

Psychiatric Disorders

Insomnia

Nervousness

Reproductive System and Breast Disorders

Menstrual disorder

Respiratory, Thoracic and Mediastinal Disorders

Epistaxis

Skin and Subcutaneous Tissue Disorders

Alopecia

Dermatitis

Erythema

Erythema multiforme

Pruritus

Rash

Urticaria

Xeroderma

Vascular Disorders

Orthostatic hypotension

Post-marketing Experience

Adverse drug reactions first identified during postmarketing experience with NIZORAL Tablets are presented in **Table 3**. Unlike for clinical trials, precise frequencies cannot be determined from spontaneous reports. The frequency for these events is therefore unknown.

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with NIZORAL Tablets

Blood and the Lymphatic System Disorders

Very rare Thrombocytopenia

Immune System Disorders

Very rare Allergic conditions including anaphylactic shock, anaphylactic reaction and angioneurotic oedema

Endocrine Disorders

Very rare Adrenocortical insufficiency

Nervous System Disorders

Very rare Reversible intracranial pressure increased (e.g. papilloedema, fontanelle bulging in infants)

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** section)

Skin and Subcutaneous Tissue Disorders

Very rare Photosensitivity

Musculoskeletal, Connective Tissue and Bone Disorders

Very rare Arthralgia

Reproductive System and Breast Disorders

Very rare Erectile dysfunction, with doses higher than the recommended therapeutic dose of 200 or 400mg daily azoospermia

At the therapeutic dosage level of 200 mg once daily, a transient decrease in the plasma levels of testosterone can be observed. Testosterone levels normalise within 24 hours. During long-term therapy at this dosage, testosterone levels do not usually differ from controls.

INTERACTIONS

Effect of other medicines on ketoconazole

Medicines affecting the absorption of ketoconazole:

Drugs that reduce the gastric acidity impair the absorption of ketoconazole (see **WARNINGS AND PRECAUTIONS** section).

Medicines affecting the metabolism of ketoconazole:

Ketoconazole is mainly metabolised through CYP3A4. Therefore, CYP3A4-inducing medicines such as rifampicin, rifabutin, carbamazepine, isoniazid, nevirapine and phenytoin significantly reduce the bioavailability of ketoconazole. The combination of ketoconazole with potent enzyme inducers is not recommended.

Ritonavir increases the bioavailability of ketoconazole. Therefore when it is given concomitantly, a dose reduction of ketoconazole should be considered.

Effects of ketoconazole on the metabolism of other medicines

Ketoconazole can inhibit the metabolism of medicines metabolised by certain hepatic P450 enzymes, especially of the CYP 3A family. This can result in an increase and/or a prolongation of their effects, including adverse effects. The concomitant administration of a number of such medicines with NIZORAL tablets are contraindicated (see **CONTRAINDICATIONS** section).

When co-administered with oral ketoconazole, the following medicines should be used with caution, and their plasma levels, effects or side effects should be monitored. The dosage of these medicines, if coadministered with ketoconazole, may need to be reduced:

- Oral anticoagulants
- HIV protease inhibitors, such as indinavir, saquinavir
- Certain antineoplastic agents, such as vinca alkaloids, busulphan, docetaxel, erlotinib and imatinib
- CYP3A4 metabolised calcium channel blockers, such as dihydropyridines and probably verapamil
- Certain immunosuppressive agents, such as cyclosporin, sirolimus (also known as rapamycin) and tacrolimus
- Certain CYP3A4 metabolised HMG-CoA reductase inhibitors such as atrovastatin
- Certain glucocorticoids such as budesonide, fluticasone, dexamethasone and methylprednisolone
- Digoxin (via inhibition of P-glycoprotein)
- Alprazolam
- Carbamazepine
- Cilostazol
- Buspirone
- Alfentanil
- Fentanyl
- Midazolam IV
- Sildenafil
- Repaglinide
- Brotizolam
- Rifabutin
- Tolterodine
- Trimetrexate
- Ebastine
- Eletriptan
- Reboxetine
- Quetiapine
- Solifenacin.

Exceptional cases have been reported of a disulfiram-like reaction to alcohol, characterised by flushing, rash, peripheral oedema, nausea and headache. All symptoms completely resolve within a few hours.

OVERDOSAGE

Symptoms:

Adverse drug reactions reported by patients taking high doses of NIZORAL are available in 6 clinical trials in a total of 459 patients where NIZORAL was administered at doses of 1,200 mg daily either in tablet form or as an oral suspension. The most commonly reported adverse drug reactions were nausea (27.2%), fatigue (including somnolence and lethargy) (14.2%), vomiting (12.6%), gastrointestinal pain (including abdominal discomfort, gastrointestinal disorder, stomach discomfort) (12.0%), anorexia (including weight decreased, decreased appetite) (7.4%), flushing (including hyperhidrosis) (6.3%), oedema (5.7%), gynaecomastia (4.8%), rash (including eczema, purpura, dermatitis) (3.3%), diarrhoea (2.2%), headache (2.0%), dysgeusia (1.3%), and alopecia (1.1%).

Treatment:

In the event of acute accidental overdosage, treatment consists of supportive and symptomatic measures. Within the first hour after ingestion, activated charcoal may be administered. Gastric lavage may be performed if considered appropriate.

Poisons Information Centre telephone numbers are:

- Australia: 13 11 26
- New Zealand: 0800 POISON or 0800 764 766

FURTHER INFORMATION

Actions

Ketoconazole is a synthetic imidazole dioxolane derivative with a fungicidal or fungistatic activity against dermatophytes, yeasts (*Candida*, *Pityrosporum*, *Torulopsis*, *Cryptococcus*), dimorphic fungi and eumycetes. Ketoconazole is less sensitive to *Aspergillus spp.*, *Sporothrix schenckii*, some *Dematiaceae*, *Mucor spp.* and other phycomycetes, except *Entomophthorales*.

Ketoconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the membrane.

Pharmacokinetics

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

Excipients

NIZORAL tablets contain maize starch, lactose, povidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Other

Ketoconazole has been tested in a standard battery of non-clinical safety studies.

Hepatotoxic effects were seen in a twelve month repeated dose dog study. Slight pathological changes in the kidneys, adrenals, and ovaries were noted in an 18 month repeated dose rat study. In addition, female rats showed an increase in bone fragility. The No Observed Adverse Effect Level (NPAEL) in both studies was 10mg/kg/day.

In reproduction studies, at very high maternally toxic doses (80mg/kg/day and higher) ketoconazole impaired female fertility in the rat and produced embryotoxic and teratogenic (oligodactylia and syndactylia) effects in pups. At 40mg/kg in rats and rabbits, ketoconazole was devoid of embryotoxicity, teratogenicity and effects on fertility. No teratogenic effects were observed in mice at any dose level tested to a maximum of 160mg/kg.

Ketoconazole is not carcinogenic or genotoxic.

PHARMACEUTICAL PRECAUTIONS

Shelf Life

3 years when stored below 25°C.

Special Precautions for Storage

Store in a dry place.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

Blisters in a carton of 30 tablets.

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