NAME OF THE MEDICINAL PRODUCT
NIZORAL Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 mg ketoconazole.
For excipients, see List of Excipients

PHARMACEUTICAL FORM
White, circular, flat bevel-edged, half-scored tablet

CLINICAL PARTICULARS
Therapeutic Indications
Because of the risk for serious hepatic toxicity, 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.
Indications are:
- Infections of the skin, hair, and mucosa, induced by dermatophytes and/or yeasts that cannot be treated topically because of the site or extent of the lesion, or deep infection of the skin.
- Dermatophytosis
- Pityriasis versicolor
- Malassezia folliculitis
- Cutaneous candidosis
- Chronic mucocutaneous candidosis
- Oropharyngeal and esophageal candidosis
- Chronic, recurrent vaginal candidosis

Systemic fungal infections
Ketoconazole does not penetrate well in the CNS. Therefore, fungal meningitis should not be treated with oral ketoconazole.
- Paracoccidioidomycosis
- Histoplasmosis
- Coccidioidomycosis
- Blastomycosis

Posology and Method of Administration
NIZORAL should be taken during meals for maximal absorption.
Infections of the skin, hair, and mucosa induced by dermatophytes and/or yeasts, and systemic infections, that cannot be treated topically because of the site or the extent of the lesion or deep infection of the skin:
Adults
- One tablet (= 200 mg) once daily with a meal. When no adequate response is obtained with this dose, the dose should be increased to 2 tablets (= 400 mg) once daily.
- Adults with vaginal candidosis: two tablets (= 400 mg) once daily with a meal.

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

- Children weighing more than 30 kg: same as for adults.

The usual duration of treatment is:

- Vaginal candidosis: 5 consecutive days;
- Skin mycosis 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;
- Paracoccidioidomycosis, histoplasmosis, coccidioidomycosis: the usual duration of therapy is 6 months.

For all indications, 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, 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.

Special Patient Population: Hepatic Impairment (see Contraindications)

Contraindications

NIZORAL tablets are contraindicated in the following situations:

- In patients with a known hypersensitivity to ketoconazole or to any of the excipients.
- In patients with acute or chronic liver disease.
- Co-administration of the CYP3A4 substrates astemizole, bepridil, cisapride, disopyramide, dofetilide, halofantrine, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertinidole or terfenadine, with NIZORAL tablets is contraindicated since increased plasma concentrations of these medicinal products can lead to QT prolongation and rare occurrences of torsades de pointes.
- Co-administration of domperidone is contraindicated since the combination can lead to QT prolongation.
- Co-administration of triazolam and oral midazolam.
- Co-administration of CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin and lovastatin.
- Co-administration of ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)
- Co-administration of nisoldipine
- Co-administration of eplerenone
- Co-administration of irinotecan
- Co-administration of everolimus

See also Interaction with other medicinal products and other forms of interaction.

Special Warnings and Special Precautions for Use

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 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 (see Undesirable effects). 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.

Monitor liver function in all patients receiving treatment with NIZORAL 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 testing should be conducted.

Monitoring of hepatic function

Monitor liver function in all patients receiving treatment with NIZORAL tablets. Monitor liver function, prior to treatment to rule out acute or chronic liver disease (see Contraindications), at frequent and regular intervals during treatment, 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.

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

Monitoring of adrenal function

In volunteers on 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, in patients under prolonged periods of stress (major surgery, intensive care, etc.),and in patients on prolonged therapy presenting signs and symptoms suggestive of adrenal insufficiency.

Pediatric use

Documented use of NIZORAL tablets in children weighing less than 15 kg is very limited. Therefore, it is not recommended to administer NIZORAL tablets to small children.

Reduced gastric acidity

Absorption is impaired when the gastric acidity isreduced. In patients also receiving acid neutralizing medicines (e.g. aluminum hydroxide) these should be administered 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. H_2-antagonists, proton pumpinhibitors) it is advisable to administer NIZORAL tablets with a cola beverage.

Drug interaction potential

NIZORAL has a potential for clinically important drug interactions (see Interaction with other medicinal products and other forms of interaction).

Interaction with Other Medicinal Products and Other Forms of Interaction

1. Drugs affecting the absorption of ketoconazole

Drugs that reduce the gastric acidity impair the absorption of ketoconazole (see Special Warnings and Special Precautions for Use).

2. **Drugs affecting the metabolism of ketoconazole**:
   Ketoconazole is mainly metabolized through the cytochrome CYP3A4.
   Enzyme-inducing drugs 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.

3. **Effect of ketoconazole on the metabolism of other drugs:**
   Ketoconazole can inhibit the metabolism of drugs metabolized 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.

Examples include:

Drugs that are contraindicated during treatment with NIZORAL tablets *(see Contraindications):*

- Co-administration of the CYP3A4 substrates, astemizole, bepridil,cisapride, disopyramide, dofetilide, halofantrine, levacetylmethadol (levomethadyl), mizolastine, pimozide quinidine, sertindole or terfenadine with NIZORAL tablets is contraindicated since increased plasma concentrations of these medicinal products can lead to QT prolongation and rare occurrences of torsades de pointes.
- Co-administration of domperidone is contraindicated since the combination can lead to QT prolongation.
- Co-administration of triazolam and oral midazolam
- Co-administration of CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin and lovastatin
- Co-administration of ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).
- Co-administration of nisoldipine
- Co-administration of eplerenone
- Co-administration of irinotecan
- Co-administration of everolimus

When co-administered with oral ketoconazole the following drugs should be used with caution, and their plasma concentration, and effects or advers effects should be monitored. Their dosage, if co-administered with ketoconazole, should be reduced if necessary. This should be considered when prescribing concomitant medication.

Examples include

- 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 the dihydropyridines and probably verapamil;
- Certain immunosuppressive agents: cyclosporine, tacrolimus, rapamycin (also known as sirolimus);

- Certain CYP3A4 metabolized HMG-CoA reductase inhibitors such as atorvastatin;
- Certain glucocorticoids such as budesonide, fluticasone, dexamethasone and methylprednisolone;
- Digoxin (via inhibition of P-glycoprotein);
- Others alfentanil, alprazolam, brotizolam, buspirone, carbamazepine, cilostazol, ebastine, eletriptan, fentanyl, midazolam IV, quetiapine, reboxetine, repaglinide, rifabutin, , sildenafil, solifenacin, tolterodine, trimetrexate.

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

Pregnancy and lactation

Use during pregnancy

There is limited information on the use of NIZORAL tablets during pregnancy. Animal studies have shown reproductive toxicity (see Preclinical Safety Data). The potential risk to humans is unknown. Therefore, NIZORAL tablets should not be used during pregnancy unless the potential benefit to the mother outweighs the possible risk to the fetus.

Use during lactation

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

Effects on Ability to Drive and Use Machines

No effects have been observed.

Undesirable 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 ≥1% of NIZORAL Tablets-treated subjects are shown in Table 1

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

System Organ Class	**%**
Preferred Term	
Gastrointestinal Disorders	
Abdominal pain	1.2
Diarrhea	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 included in Table 3. In this table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000, including isolated reports

In table 3 ADRs are presented by frequency category based on spontaneous reporting rates

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with NIZORAL Tablets by Frequency Category Estimated from Spontaneous Reporting Rates	
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 Special Warnings and Special Precautions for Use)
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

Overdose

There is no known antidote to ketoconazole.

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 overdose, 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic classification: Antimycotics for systemic use, imidazole derivatives

Ketoconazole is a synthetic imidazole dioxolane derivative with a fungicidal or fungistatic activity against dermatophytes, yeasts (*Candida, Malassezia, Torulopsis, Cryptococcus*), dimorphic fungi and eumycetes. Less sensitive are: *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.
Data from some clinical PK/PD studies and drug interaction studies suggest that oral dosing with ketoconazole at 200 mg twice daily for 3-7 days can result in a small increase of the QTc interval: a mean maximum increase of about 6 to 12 msec was seen at ketoconazole peak plasma levels, about 1-4 hours after ketoconazole administration. This small prolongation of the QT interval, however, is not considered to be clinically relevant.
At the therapeutic dosage of 200 mg once daily, a transient decrease in the plasma concentrations of testosterone can be observed. Testosterone concentrations return to pre-dose concentrations within 24 hours after administration of ketoconazole. During long-term therapy at this dosage, testosterone concentrations are usually not significantly different from controls.
In volunteers on daily doses of 400 mg and more, ketoconazole has been shown to reduce the cortisol response to ACTH stimulation (see Special Warnings and Special Precautions for Use).

Pharmacokinetic properties

Absorption

Ketoconazole is a weak dibasic agent and thus requires acidity for dissolution and absorption. Mean peak plasma concentrations of approximately 3.5 µg/mL are reached within 1 to 2 hours, following oral administration of a single 200 mg dose taken with a meal.

Distribution

In vitro, the plasma protein binding is about 99% mainly to the albumin fraction. Ketoconazole is widely distributed into tissues; however, only a negligible proportion reaches the cerebrospinal fluid.

Metabolism

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, by hepatic microsomal enzymes. In addition, oxidative O-dealkylation and aromatic hydroxylation does occur. Ketoconazole has not been demonstrated to induce its own metabolism.

Elimination

Elimination from plasma is biphasic with a half-life of 2 hours during the first 10 hours and 8 hours thereafter. 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.

Conditions in special populations

In patients with hepatic or renal insufficiency the overall pharmacokinetics of ketoconazole was not significantly different when compared with healthy subjects. (see Contraindication and Special Warning and Special Precautions for Use.

Preclinical Safety Data

Ketoconazole has been tested in a standard battery of non-clinical safety studies. Hepatotoxic effects were seen in a 12-month repeated dose dog study. Slight pathological changes in the kidney, 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 (NOAEL) in both these studies was 10 mg/kg/day. In reproduction studies, at very high, maternally toxic doses (80 mg/kg/day and higher), ketoconazole impaired female fertility in the rat, and produced embryotoxic and teratogenic (oligodactylia and syndactylia) effects in pups. At 40 mg/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 up to a maximum of 160 mg/kg.
Ketoconazole is not carcinogenic or genotoxic.
Electrophysiological studies have shown that ketoconazole inhibits the rapidly activating component of the cardiac delayed rectifier potassium current, prolongs the action potential duration, and may prolong the QT interval.

PHARMACEUTICAL PARTICULARS

List of Excipients

The inactive ingredientsof the tablets are maize starch, lactose, polyvidone, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Incompatibilities

None known.

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

Do not store above 30°C.
The tablets must be stored in a dry place.
Keep out of reach of children.

Nature and Contents of Container

Nizoral is available as tablets, containing 200 mg of ketoconazole, supplied in blister packs.

Instructions for Use and Handling <and Disposal>

Not applicable

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

December 2010