NIZORAL® Tablets
Janssen

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, 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

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 is reduced. 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. H₂-antagonists, proton pump inhibitors) 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 dihydrolergotamine, 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 adverse 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;
Table 1. Adverse Drug Reactions Reported in ≥1% of 4735 NIZORAL Tablets-treated Subjects in 92 Clinical Trials

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>2.5</td>
</tr>
<tr>
<td>Hepato-biliary Disorders</td>
<td>Hepatic function abnormal</td>
<td>1.2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>2.4</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Disorders</td>
<td>Gynaecomastia</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Photophobia</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain upper</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Dysgeusia</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
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<tr>
<td></td>
<td>Flatulence</td>
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<tr>
<td></td>
<td>Tongue discolouration</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Hot flush</td>
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<tr>
<td></td>
<td>Malaise</td>
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<tr>
<td></td>
<td>Oedema peripheral</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Hepato-biliary Disorders</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Anaphylactoid reaction</td>
</tr>
<tr>
<td>Investigations</td>
<td>Platelet count decreased</td>
</tr>
</tbody>
</table>

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 3. Adverse Drug Reactions Identified During Postmarketing Experience with NIZORAL Tablets by Frequency Category Estimated from Spontaneous Reporting Rates**

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the Lymphatic System Disorders</strong></td>
<td>Very rare</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td>Very rare</td>
<td>allergic conditions including anaphylactic shock, anaphylactic reaction and angioneurotic oedema</td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td>Very rare</td>
<td>adrenocortical insufficiency</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td>Very rare</td>
<td>reversible intracranial pressure increased (e.g. papilloedema, fontanelle bulging in infants)</td>
</tr>
<tr>
<td><strong>Hepato-biliary Disorders</strong></td>
<td>Very rare</td>
<td>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)</td>
</tr>
<tr>
<td><strong>Skin &amp; Subcutaneous Tissue Disorders</strong></td>
<td>Very rare</td>
<td>photosensitivity</td>
</tr>
<tr>
<td><strong>Musculoskeletal, Connective Tissue and Bone Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Very rare</td>
<td>erectile dysfunction, with doses higher than the recommended therapeutic dose of 200 or 400 mg daily azoospermia</td>
</tr>
<tr>
<td><strong>Post-marketing experience</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

**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, gastrentestinal 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%),
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 ingredients of 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.

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December 2010