SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LOZANOC 50 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 50 mg itraconazole.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard. Size 1

Opaque blue with *i*-50 printed in black on the capsule

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Superficial mycoses

Itraconazole is indicated – if external treatment is not effective or not appropriate – for the treatment of the following fungal infections: dermatomycoses (e.g. tinea corporis, tinea cruris, tinea pedis, tinea manus) and Pityriasis versicolor

Systemic mycoses

Itraconazole is indicated for the treatment of systemic mycoses, such as candidiasis, aspergillosis, and histoplasmosis

Consideration should be given to official guidance on the appropriate use of antimycotic agents.

4.2 Posology and method of administration

LOZANOC 50 mg hard capsules are for oral administration and can be taken with or without food.

One hard capsule of LOZANOC 50 mg corresponds to one 100 mg hard capsule of conventional itraconazole hard capsules. The recommended dose for LOZANOC is

therefore half the recommended dose for conventional itraconazole hard capsules (see Section 5.1 and Section 5.2).

The LOZANOC treatment schedules in adults for each indication are as follows:

Superficial mycoses (of skin, mucosae, eyes)		
Indication	**LOZANOC 50 mg Capsule Hard Dosage**	**Duration of treatment**
Pityriasis versicolor	2 capsules once daily	7 days
Tinea corporis, Tinea cruris	1 capsule once daily	2 weeks
Dermatomycosis of palms and soles (tinea manus, tinea pedis)	1 capsule once daily	4 weeks
Dermatomycosis of nails (tinea unguium)	2 capsules once daily	12 weeks
In some immunosuppressed patients, e.g. with neutropenia, AIDS or after organ transplantation, the bioavailability of itraconazole may be lowered. Doubling the dose may be indicated.		

Itraconazole remains substantially longer in the skin than in the blood. Optimal healing is thus achieved 2-4 weeks after withdrawing Itraconazole in case of mycoses of the skin.

Systemic mycoses			
Indication	**LOZANOC 50 mg Hard Capsule Dosage**	**Duration of treatment[1)]**	**Notes**
Aspergillosis	2 capsules *once daily*	2-5 months	In invasive or disseminated disease, increase to 2 capsules twice daily (in the morning and in the evening)
Candidiasis	1-2 capsules once daily	3 weeks-7 months	In invasive or disseminated disease, increase to 2 capsules twice daily (in the morning and in the evening)
Histoplasmosis	2 capsules once daily up to twice daily (in the morning and in the evening)	8 months	-

1) The duration of treatment should be adjusted depending on clinical efficacy.

Use in children

Not recommended. See 4.4 Special warnings and special precautions for use.

In Elderly

Not recommended. See 4.4 Special warnings and special precautions for use.

Use in patients with renal impairment

The oral bioavailability of itraconazole may be lower in patients with renal insufficiency, a dose adjustment may be considered. See 4.4 Special warnings and special precautions for use.

Use in patients with hepatic impairment

Itraconazole is predominantly metabolised by the liver. The terminal half-life of itraconazole in cirrhotic patients is somewhat prolonged. The oral bioavailability in cirrhotic patients is somewhat decreased. A dose adjustment may be considered. See 4.4 Special warnings and special precautions for use.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Coadministration of the following drugs is contraindicated with itraconazole (see section 4.5):

- CYP3A4 metabolised substrates that can prolong the QT-interval e.g., astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with itraconazole. Coadministration may result in increased plasma concentrations of these substrates which can lead to QTc prolongation and rare occurrences of torsades de pointes.
- CYP3A4 metabolised HMG-CoA reductase inhibitors such as lovastatin and simvastatin
- Potent CYP3A4 inhibitors such as dronedarone
- Drugs which are substrates for the efflux transporter P-glycoprotein, such as dabigatranTriazolam and oral midazolam
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)
- Eletriptan
- Nisoldipine
- Itraconazole should not be administered for non-life threatening indications to patients receiving disopyramide or halofantrine.

• Itraconazole should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life threatening or other serious infections (see section 4.4).
• Itraconazole must not be used during pregnancy for non-life-threatening indications (see section 4.6).

4.4 Special warnings and precautions for use

One hard capsule of LOZANOC 50 mg corresponds to one 100 mg hard capsule of conventional itraconazole hard capsules. The recommended dose for LOZANOC is therefore half the recommended dose for conventional itraconazole hard capsules.

Cross-hypersensitivity

There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing itraconazole hard capsules to patients with hypersensitivity to other azoles.

Cardiac effects

In a healthy volunteer study with itraconazole IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed.

Itraconazole has been shown to have a negative inotropic effect and itraconazole has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.

Itraconazole should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dose and duration of treatment (e.g. total daily dose), and individual risk factors for congestive heart failure. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, itraconazole should be discontinued.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be exercised when co-administering itraconazole and calcium channel blockers (see section 4.5) due to an increased risk of congestive heart failure.

Hepatic effects

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of itraconazole. Some of these cases involved patients with no pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking hepatotoxic drugs. Some patients had no obvious risk factors for liver disease. Some of these cases were observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving itraconazole treatment. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. In these patients treatment should be stopped immediately and liver function testing conducted. In patients with raised liver enzymes or active liver disease, 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 liver enzyme monitoring is necessary.

Impact of reduced gastric acidity

In vitro dissolution studies have demonstrated that the dissolution of itraconazole from LOZANOC is not affected by increased pH. Therefore patients taking drugs that reduce gastric acid or who are otherwise achlorhydric are unlikely to have a reduction in bioavailability of itraconazole from LOZANOC in contrast to conventional itraconazole.

Use in children

Clinical data on the use of itraconazole in paediatric patients is limited. Itraconazole should not be used in paediatric patients unless the potential benefit outweighs the potential risks.

Use in elderly

Clinical data on the use of itraconazole in elderly patients is limited. Itraconazole should not be used in these patients unless the potential benefit outweighs the potential risks.

Hepatic impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population. (See section 5.2).

Renal impairment

The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. Dose adaptation may be considered.

Hearing Loss

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see 4.3 and 4.5). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Immunocompromised patients

In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), the oral bioavailability of itraconazole may be decreased.

Patients with immediately life-threatening systemic fungal infections

Due to the pharmacokinetic properties (see section 5.2), itraconazole is not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

Patients with AIDS

In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal or non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Interaction Potential

Itraconazole has a potential for clinically important drug interactions. (See section 4.5).

Itraconazole should not be used within 2 weeks after discontinuation of treatment with CYP 3A4 inducing agents (rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine, Hypericum perforatum (St. John´s wort)). The use of itraconazole with these drugs may lead to subtherapeutic plasma levels of itraconazole and thus treatment failure.

Cross-resistant strains

In systemic candidosis, if fluconazole-resistant strains of Candida species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of itraconazole therapy.

4.5 Interaction with other medicinal products and other forms of interaction

1. Drugs affecting the metabolism of itraconazole:

Itraconazole is mainly metabolised through the cytochrome CYP3A4. Interaction studies have been performed with rifampicin, rifabutin and phenytoin, which are potent inducers of CYP3A4. Since the bioavailability of itraconazole and hydroxy-itraconazole was decreased in these studies to such an extent that efficacy may be largely reduced, the combination of itraconazole with these potent enzyme inducers is not recommended. No formal study data are available for other enzyme inducers, such as carbamazepine, phenobarbital and isoniazid, but similar effects should be anticipated.

Potent inhibitors of this enzyme such as ritonavir, indinavir, clarithromycin and erythromycin may increase the bioavailability of itraconazole.

2. Effects of itraconazole on the metabolism of other drugs:

Itraconazole can inhibit the metabolism of drugs metabolized by the cytochrome 3A family. This can result in an increase and/or a prolongation of their effects, including side effects. When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism. After stopping treatment, itraconazole plasma concentrations decline gradually, depending on the dose and duration of treatment (see 5.2 Pharmacokinetic Properties). This should be taken into account when the inhibitory effect of itraconazole on co-administered drugs is considered.

Itraconazole is also reported to inhibit gastric P-glycoprotein (P-gp), a transmembrane efflux pump that can limit systemic exposure through inhibition of gastrointestinal absorption. As such, inhibition of P-gp by itraconazole can increase the absorption of drugs affected by this transport system.

Examples are:

The following drugs are contraindicated with itraconazole:

- Astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole or terfenadine are contraindicated with itraconazole since co-administration may result in

increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsades de pointes.

- CYP3A4 metabolised HMG-CoA reductase inhibitors such as lovastatin and simvastatin.
- Potent CYP3A4 inhibitors such as dronedarone.
- Drugs which are substrates for the efflux transporter P-glycoprotein, such as dabigatran.
- Triazolam and oral midazolam.
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).
- Eletriptan
- Nisoldipine

Caution should be exercised when co-administering itraconazole with calcium channel blockers due to an increased risk of congestive heart failure. In addition to possible pharmacokinetic interactions involving the drug metabolising enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole.

The following drugs should be used with caution, and their plasma concentrations, effects or side effects should be monitored. Their dosage, when co-administered with itraconazole, should be reduced if necessary:

- Oral anticoagulants, such as warfarin
- HIV protease inhibitors such as ritonavir, indinavir, saquinavir
- Certain antineoplastic agents such as vinca alkaloids, busulfan, docetaxel and trimetrexate
- CYP3A4 metabolised calcium channel blockers such as dihydropyridines and verapamil
- Certain immunosuppressive agents: ciclosporin, tacrolimus, rapamycin (also known as sirolimus)
- Certain CYP3A4 metabolised HMG-CoA reductase inhibitors such as atorvastatin.
- Certain glucocorticoids such as budesonide, dexamethasone, fluticasone and methyl prednisolone
- Digoxin
- Others: carbamazepine, cilostazol, buspirone, disopyramide, alfentanil, alprazolam, brotizolam, midazolam IV, rifabutin, ebastine, fentanyl, halofantrine, repaglinide and reboxetine. The importance of the concentration increase and the clinical relevance of these changes during co-administration with itraconazole remain to be established.

No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed. No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

3. Effect on protein binding:

In vitro studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indometacin, tolbutamide or sulphadimidine.

4.6 Fertility, pregnancy and lactation

Fertility

There is no evidence of a primary influence on fertility (see section 5.3).

Pregnancy

There is limited information on the use of itraconazole during pregnancy. During post-marketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations. A causal relationship with itraconazole has not been established. However, epidemiological data on exposure to itraconazole during the first trimester of pregnancy -mostly in patients receiving short-term treatment for vulvovaginal candidosis- did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.

In animal studies itraconazole has shown reproduction toxicity (see section 5.3).

Itraconazole capsules must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see section 4.3).

Women of child bearing potential

Itraconazole is not recommended in women of childbearing potential not using contraception. Effective contraception should be continued until the next menstrual period following the end of itraconazole therapy.

Lactation

A very small amount of itraconazole is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to abstain from itraconazole, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss (see Section 4.8), which may occur in some instances, must be taken into account.

4.8 Undesirable effects

Undesirable effects listed below have been reported in clinical trials with itraconazole capsules and/or from spontaneous reports from post-marketing experience for all itraconazole formulations.

In clinical trials involving 2104 itraconazole-treated patients in the treatment of dermatomycoses or onychomycosis, the most frequently reported adverse experiences were of gastrointestinal, dermatological, and hepatic origin.

The table below presents adverse drug reactions by System Organ Class. Within each System Organ Class, the adverse drug reactions are presented by incidence, using the following convention:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1,000 to < 1/100)

Rare (≥ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000)

Not known (cannot be estimated from the available data)

System Organ Class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1000 to < 1/100	**Rare** ≥ 1/10 000 to < 1/1000	**Not known** (frequency cannot be estimated from the available postmarketing data)
Blood and lymphatic system disorders			Leukopenia	Neutropenia, thrombocytopenia
Immune system disorders		Hypersensitivity*		Anaphylactic reaction, anaphylactoid reaction, angioneurotic oedema, serum sickness
Metabolism and nutrition disorders				Hypokalemia, hypertriglyceridemia
Nervous system disorders		Headache, dizziness, paraesthesia	Hypoaesthesia	Peripheral neuropathy*
Eye disorders			Visual disturbance	Vision blurred and diplopia
Ear and labyrinth disorders			Tinnitus	Transient or permanent hearing loss*
Cardiac disorders				Congestive heart failure*
Respiratory, thoracic and mediastinal disorders				Pulmonary oedema

Gastrointestinal disorders	Abdominal pain, nausea	Vomiting, diarrhoea, constipation, dyspepsia, dysgeusia, flatulence	Pancreatitis	
Hepatobiliary disorders		Hyperbilirubinaemia, Alanine aminotransferase increased, Aspartate aminotransferase increased	Hepatic enzyme increased	Acute hepatic failure*, hepatitis, hepatotoxicity*
Skin and subcutaneous tissue disorders	Rash	Urticaria, alopecia, pruritus		Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, photosensitivity
Musculoskeletal and connective tissue disorders				Myalgia, arthralgia
Renal and urinary disorders			Pollakiuria	Urinary incontinence
Reproductive system and breast disorders		Menstrual disorder		Erectile dysfunction
General disorders and administration site conditions		Oedema	Pyrexia	

* see section 4.4.

4.9 Overdose

In the event of overdosage, patients should be treated symptomatically with supportive measures. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate. No specific antidote is available. Itraconazole cannot be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotic for systemic use, triazole derivative.

ATC code: J02AC02

Mode of action

Itraconazole inhibits fungal 14α-demethylase, resulting in a depletion of ergosterol and disruption of membrane synthesis by fungi.

Pharmacokinetic / Pharmacodynamic relationship

The most important parameter for itraconazole is the AUC/ MIC ratio. This PK-PD parameter demonstrates that LOZANOC 50 mg achieves the AUC/MIC ratio which should be greater than 25 for optimal efficacy in both the fed and fasted state for the organisms relevant to the indicated superficial and systemic mycoses (see section 4.1). Therefore, LOZANOC can be considered a therapeutic alternative to the innovator product Sporanox, in the treatment of these indications.

Mechanism(s) of resistance

Resistance of fungi to azoles appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are:

- Over-expression of ERG11, the gene that encodes 14-alpha-demethylase (the target enzyme)
- Point mutations in ERG11 that lead to decreased affinity of 14-alpha-demethylase for itraconazole
- Drug-transporter over-expression resulting in increased efflux of itraconazole from fungal cells (i.e., removal of itraconazole from its target)
- Cross-resistance. Cross-resistance amongst members of the azole class of drugs has been observed within Candida species though resistance to one member of the class does not necessarily confer resistance to other azoles.

Breakpoints

Breakpoints for itraconazole have not yet been established for fungi using EUCAST methods.

Using CLSI methods, breakpoints for itraconazole have only been established for Candida species from superficial mycotic infections. The CLSI breakpoints are: susceptible ≤0.125 mg/L and resistant >1 mg/L.

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The in vitro susceptibility of fungi to itraconazole depends on the inoculum size, incubation temperature, growth phase of the fungi, and the culture medium used. For these reasons, the minimum inhibitory concentration of itraconazole may vary widely. Susceptibility in the table below is based on MIC90 <1 mg itraconazole/L. There is no correlation between in vitro susceptibility and clinical efficacy.

Commonly susceptible species
Aspergillus spp.[2]
Blastomyces dermatitidis[1]
Candida albicans
Candida parapsilosis

Cladosporium spp.
Coccidioides immitis[1]
Cryptococcus neoformans
Epidermophyton floccosum
Fonsecaea spp. [1]
Geotrichum spp.
Histoplasma spp.
Malassezia (formerly Pityrosporum) spp.
Microsporum spp.
Paracoccidioides brasiliensis[1]
Penicillium marneffei[1]
Pseudallescheria boydii
Sporothrix schenckii
Trichophyton spp.
Trichosporon spp.
Species for which acquired resistance may be a problem
Candida glabrata[3]
Candida krusei
Candida tropicalis[3]
Inherently resistant organisms
Absidia spp.
Fusarium spp.
Mucor spp.
Rhizomucor spp.
Rhizopus spp.
Scedosporium proliferans
Scopulariopsis spp.

[1] These organisms may be encountered in patients who have returned from travel outside Europe.

[2] Itraconazole-resistant strains of Aspergillus fumigatus have been reported.

[3] Natural intermediate susceptibility.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of itraconazole have been investigated in healthy subjects after single and multiple dosing.

Absorption

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 - 6 hours following an oral dose

In a clinical trial comparing single doses of LOZANOC 50 mg hard capsules to conventional 100 mg itraconazole hard capsules, both taken with a full meal, the observed relative bioavailability (Frel) of itraconazole of the LOZANOC 50 mg formulation was 181%. In this trial, the Frel for the LOZANOC 50 mg hard capsule formulation when taken in the fasted versus the fed state was 124%, whereas for the conventional 100 mg hard capsule formulation the Frel was 156%.

In a replicate-designed clinical trial comparing two single doses of LOZANOC 50 mg hard capsules to two single doses of conventional 100 mg itraconazole hard capsules, both taken with a full meal, within-subject variability in total exposure was considerably lower for the LOZANOC 50 mg formulation than for the conventional 100 mg itraconazole formulation, with values of 27.8% and 51.2% for AUC0-tlast and 22.2% and 47.4% for AUC0-inf, respectively. There was no overlap in the 90% CI ranges obtained for the two formulations at each AUC measure, therefore the difference in within-subject variability, in the order of 50%, was statistically significant at the 90% level.

Distribution

Most of the itraconazole in plasma is bound to protein (99.8%) with albumin being the main binding component (99.6% for the hydroxy- metabolite). It has also a marked affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug.

Itraconazole is distributed in a large apparent volume in the body (> 700 L), suggesting its extensive distribution into tissues: Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma. Brain to plasma ratios were about 1 as measured in beagle dogs. The uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma.

Biotransformation

Itraconazole is extensively metabolised by the liver into a large number of metabolites. One of the main metabolites is hydroxyl-itraconazole, which has in vitro antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxy-itraconazole are about twice those of itraconazole.

As shown in in vitro studies, CYP 3A4 is the major enzyme that is involved in the metabolism of itraconazole.

Elimination

Itraconazole is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with faeces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas faecal excretion of unchanged drug varies between 3-18% of the dose. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Linearity/non-linearity

As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with Cmax and AUC values 4-7 fold higher than those seen after a single dose. The mean elimination half-life of itraconazole is about 40 hours after repeated dosing.

Special Populations

Hepatic Insufficiency: Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population.

Renal Insufficiency: Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when the drug is administered in this patient population.

5.3 Preclinical safety data

Nonclinical data on itraconazole revealed no indications for geno toxicity, primary carcinogenicity or impairment of fertility. At high doses, effects were observed in the adrenal cortex, liver and the mononuclear phagocyte system but appear to have a low relevance for the proposed clinical use. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats and mice at high doses. A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, and in rats, decreased bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: Hypromellose phthalate, sodium starch glycolate (type A), silica colloidal anhydrous, magnesium stearate.

Hard capsule shell: gelatin, Brillant Blue FCF (E133) and titanium dioxide (E171).

Printing Ink: Black (SW-9008), consisting of shellac, potassium hydroxide, black iron oxide (E172), and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE Bottles: 3 years
Soft Temper Aluminium Foil (oPA/Al/PVC25/45/60) Blister Packs: 3 years
Triplex (PVC/PE/PVdC250/30/90) Blister Packs: 2 years

6.4 Special precautions for storage

HDPE Bottles
This medicinal product does not require any special temperature storage conditions
Store in the original package in order to protect from light and moisture.

Soft Temper Aluminium Foil blister
This medicinal product does not require any special temperature storage conditions
Store in the original package in order to protect from light and moisture.

Triplex blister
Do not store above 25°C.
Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Soft Temper Aluminium Foil blister and Triplex blister
Pack sizes: 4, 6, 7, 8, 14, 15, 18, 28, 30, 60.

HDPE Bottle with white PP child resistant cap and heat seal liner
Pack sizes: 15, 30, 60, 90.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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