1. Name of the medicinal product

Itracap100 mg Capsules

2. Qualitative and quantitative composition

One capsule contains 100 mg itraconazole.

3. Pharmaceutical form

Capsule,

4. Clinical particulars

4.1 Therapeutic indications
Itraconazole is indicated for the treatment of the following fungal infections when thought likely to be susceptible:

• Vulvovaginal candidiasis.

• Pityriasis versicolor.

• Dermatophytoses caused by organisms susceptible to itraconazole (Trichophyton spp. Microsporum spp. Epidermophyton floccosum) e.g. tinea pedis, tinea cruris, tinea corporis, tinea manuum.

• Oral candidiasis.

• Onychomycosis caused by dermatophytes and/or yeasts.

Consideration should be given to official guidance regarding the appropriate use of antifungal agents.

4.2 Posology and method of administration
Posology

Treatment schedules in adults for each indication are as follows:

Indication	**Dose**
Vulvovaginal candidiasis	200 mg twice daily for 1 day
Pityriasis versicolor	200 mg once daily for 7 days
Tinea corporis, tinea cruris	100 mg once daily for 15 days
Tinea pedis, tinea manuum	100 mg once daily for 30 days
Oral candidiasis	100 mg once daily for 14 days
Onychomycosis	200 mg once daily for 3 months

For skin infections, optimal clinical and mycological effects are reached at 1 - 4 weeks after cessation of treatment and for nail infections at 6 - 9 months after the cessation of treatment. This is because elimination of itraconazole from skin and nails is slower than from plasma.

In Acquired Immune Deficiency Syndrome and neutropenic patients: for the treatment of oral candidiasis 200 mg once daily for 14 days is recommended due to the impaired absorption of itraconazole in these patient groups.

The length of treatment for systemic fungal infections should be dictated by the mycological and clinical response to therapy.

Paediatric population:

Since clinical data on the use of itraconazole in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks.

Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes.

Elderly:

There are inadequate data on itraconazole in elderly for its use to be recommended, unless the potential benefits outweigh the risks.

Hepatic impairment:

Itraconazole is predominantly metabolised by the liver. A slight decrease in oral bioavailability in cirrhotic patients has been observed, although this was not of statistical significance. The terminal half-life was significantly increased. The dose should be adapted if necessary. Monitoring of plasma levels may be necessary.

Renal impairment:

The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. Dose adjustment may be considered. Monitoring of plasma levels may be necessary. Itraconazole cannot be removed by dialysis.

Decreased gastric acidity:

Absorption of itraconazole is impaired when gastric acidity is decreased. For information on patients with achlorhydria and patients on acid secretion suppressors or taking acid neutralising medicinal products.

Method of administration

Itraconazole is for oral administration and must be taken immediately after a meal for maximal absorption.

4.3 Contraindications
Itraconazole is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients.

Co-administration of the following substances is contraindicated with Itraconazole:

- substrates metabolized via cytochrome P450 3A4, that can prolong the QT interval, such as astemizole, bepridil, cisapride, dofetilide, levacetylmethadole (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine. Co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsade de pointes.

- HMG-CoA reductase inhibitors metabolized via cytochrome P450 3A4 such as atorvastatin, lovastatin and simvastatin

- triazolam and oral midazolam

- ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)

- eletriptan

- nisoldipine

Itraconazole must not be used during pregnancy, except in life-threatening situations.

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.

4.4 Special warnings and precautions for use
Cardiac effects

In a healthy volunteer study with intravenous itraconazole, a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. The clinical relevance of these findings to the oral formulations is unknown.

Itraconazole has been shown to have a negative inotropic effect and 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 dosing regimen (e.g., total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. 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 metabolisms of calcium channel blockers.Therefore, concurrent administration of itraconazole and calcium channel blockers should be carried out with caution.

Hepatic effects

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of itraconazole. Most of these cases involved patients who, had pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking other 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 should be 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 close liver enzyme monitoring is necessary.

Reduced gastric acidity

Absorption of itraconazole is impaired when gastric acidity is reduced. In patients also receiving acid neutralizing medicines (e.g. aluminium hydroxide) these should be administered at least 2 hours after the intake of itraconazole capsules. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (e.g., H_2-antagonists, proton pump inhibitors) it is advisable to administer itraconazole capsules with a cola beverage.

Paediatric population

Clinical data on the use of Itraconazole capsules in paediatric patients is limited. Itraconazole capsules 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.

Renal impairment

Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population. 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 sections 4.3 and 4.5). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Women of childbearing potential

Women of childbearing potential taking Itraconazole should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Itraconazole therapy.

Immunocompromised patients

In some immunosuppressed patients (e.g. in neutropenia, AIDS or after organ transplantation), 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 capsules are 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 and non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Cross-hypersensitivity

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

Neuropathy

If neuropathy occurs that may be attributable to Itraconazole, the treatment should be discontinued.

Cross-resistance

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.

Interaction potential

Itraconazole has a potential for clinically important drug interactions.

Itraconazole should not be used within 2 weeks after discontinuation of treatment with CYP3A4 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.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
1. Medicinal products influencing the absorption of itraconazole

Medicinal products that reduce the gastric acidity impair the absorption of itraconazole (see section 4.4).

2. Medicinal products affecting the metabolism of itraconazole

Itraconazole is metabolized mainly via cytochrome P450 3A4.

Interaction studies have been performed with rifampicin, rifabutin and phenytoin, which are potent enzyme 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, *Hypericum perforatum* (St John's Wort), 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.

3. Effect of itraconazole on the metabolism of other medicinal products

3.1 Itraconazole can inhibit the metabolism of medicinal products metabolized via enzymes of the cytochrome 3A family. This may result in a higher and/or prolonged action of these agents 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. This should be taken into account when the inhibitory effect of itraconazole on co-medicated drugs is considered.

Examples are:

The following medicinal products are contraindicated with itraconazole:

astemizole, bepredil, cisapride, dofetilide, levacetylmethadole (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine, since co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsade de pointes.

- HMG-CoA reductase inhibitors metabolized via cytochrome P450 3A4 such as atorvastatin, lovastatin and simvastatin

- triazolam and oral midazolam

- ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)

- nisoldipine

- eletriptan

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

The following agents should be used with caution and their plasma concentrations, effects or side effects be monitored. If necessary, their dosage should be reduced when administered concomitantly with itraconazole:

- oral anticoagulants;

- HIV protease inhibitors such as indinavir, ritonavir, saquinavir;

- certain antineoplastic agents such as busulfan, docetaxel, trimetrexate and vinca alkaloids;

- calcium channel blockers metabolized via cytochrome P450 3A4 such as dihydropyridines and verapamil;

- certain immunosuppressive agents: ciclosporin, rapamycin (also known as sirolimus) and tacrolimus;

- certain glucocorticoids such as budesonide, dexamethasone, fluticasone and methylprednisolone;

- Digoxin (via inhibition of P-glycoprotein)

- others: alfentanil, alprazolam, brotizolam, buspirone, carbamazepine, cilostazole, disopyramide, ebastine, fentanyl, halofantrine, midazolam i.v., reboxetine, repaglinide, rifabutin

3.2 No interactions between itraconazole and zidovudine (AZT) or fluvastatin have been observed.

No enzyme-inducing effects on the metabolism of ethinylestradiol and norethisterone caused by itraconazole have been observed.

4. Effect on plasma protein binding

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

4.6 Fertility, pregnancy and lactation
Pregnancy

Itraconazole must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the fetus.

In animal studies itraconazole has shown reproduction toxicity.

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.

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.

Women of childbearing potential

Women of childbearing potential taking itraconazole capsules should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of itraconazole therapy.

Breastfeeding

A very small amount of itraconazole is excreted in human milk. The expected benefits of itraconazole capsules therapy should therefore be weighed against the potential risk of breast-feeding. In case of doubt, the patient should not breast-feed.

Fertility

There was no evidence of a primary influence on fertility based on preclinical safety data.

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, 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			Dyspnoe	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, acute generalised exenthematous pustulosis, 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.

Paediatric population

The safety of itraconazole was evaluated in 250 paediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least one dose of itraconazole oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data. Based on pooled safety data from these clinical trials, the very common reported ADRs in paediatric patients were vomiting (36.0%), pyrexia (30.8%), diarrhoea (28.4%), mucosal inflammation (23.2%), rash (22.8%), abdominal pain (17.2%), nausea (15.6%), hypertension (14.0%), and cough (11.2%). The nature of

ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric patients.

4.9 Overdose
No data are available.

In the event of of an overdose, supportive measures should be employed. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

Itraconazole cannot be removed by haemodialysis.

No specific antidote is available.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.

Mechanism of action

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

Pharmacokinetic/pharmacodynamic relationship

The PK/PD relationship for itraconazole, and for triazoles in general, is poorly understood and is complicated by limited understanding of antifungal pharmacokinetics.

Mechanisms 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

Using EUCAST methods, breakpoints for itraconazole have only been established for aspergillus species. These breakpoints are given in the table below, according to EUCAST Antifungal Clinical Breakpoint Table v. 4.1, valid from 2012-03-05)

Antifungal agent	Species-related breakpoints (S≤/R>) (mg/L)					Non-species related breakpointsS≤/R>
	A. flavus	*A. fumigates*	*A. nidulans*	*A. niger*	*A. terreus*	
Itraconazole[1]	1/2	½	1/2	IE[2,3]	½	IE[3]

A. = Aspergillus

S = Susceptible, R = Resistant

1. Monitoring of itraconazole trough concentrations in patients treated for fungal infection is recommended.

2. The ECOFFs for these species are in general one step higher than for *A. fumigatus.*

3. The MIC values for isolates of *A. niger* and *A. versicolor* are in general higher than those for *A. fumigatus*. Whether this translates into a poorer clinical response is unknown.

IE = There is insufficient evidence (IE) to set breakpoints for these species.

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 MIC_{90} <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.

Paediatric population

The tolerability and safety of itraconazole was studied in the prophylaxis of fungal infections in 103 neutropenic paediatric patients aged 0 to 14 years (median 5 years) in an open-label uncontrolled phase III clinical study. Most patients (78%) were undergoing allogenic bone marrow transplantation for haematological malignancies. All patients received 5 mg/kg/day of itraconazole oral solution as a single or divided dose. Due to the design of the study, no formal conclusion with regard to efficacy could be derived. The most common adverse events considered definitely or possibly related to itraconazole were vomiting, abnormal liver function, and abdominal pain.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of itraconazole has been investigated in healthy subjects, special populations and patients after single and multiple dosing.

Absorption

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

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 hydroxy-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 feces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas fecal 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 C_{max} and AUC values 4 to 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: A pharmacokinetic study using a single 100 mg dose of itraconazole (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC were seen between these two groups. A statistically significant reduction in average C_{max} (47%) and a two fold increase in the elimination half-life (37 ± 17 versus 16 ±5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects.

Data are not available in cirrhotic patients during long-term use of itraconazole.

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.

Paediatric population

Two pharmacokinetic studies have been conducted in neutropenic children aged 6 months to 14 years in which itraconazole oral solution was administered 5 mg/kg once or twice daily. The exposure to itraconazole was somewhat higher in older children (6 to 14 years) compared to younger children. In all children, effective plasma concentrations of itraconazole were reached within 3 to 5 days after initiation of treatment and maintained throughout treatment.

5.3 Preclinical safety data
Nonclinical data on itraconazole revealed no indications for gene 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, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

6. Pharmaceutical particulars

6.1 List of excipients
Poloxamer 188

Hypromellose

Capsule shell.

Titanium dioxide (E171)

Indigo carmine (E132)

Gelatin

Quinoline yellow (E104)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Do not store above 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
Packed in Alu-Alu blister of 3x10
6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

PROMEDIX LTD

2, NINKU LINK,SECRETARIAT JUNCTION, JOS