



**National Agency for Food & Drug Administration &  
Control (NAFDAC)**

**Registration & Regulatory Affairs (R & R)  
Directorate**

**SUMMARY OF PRODUCT CHARACTERISTICS  
(SmPC) TEMPLATE**

**1. NAME OF THE MEDICINAL PRODUCT**

**ITRATOR** (Itraconazole Capsules 100 mg)

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard gelatin capsule contains:

Itraconazole Pellets

Eq. to Itraconazole BP.....100 mg

Excipients.....q.s.

Approved color used in an empty capsule shell.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Off white spherical pellets filled in a red colored cap and transparent body hard gelatin capsule of size "0".

**4. Clinical particulars**

**4.1 Therapeutic indications**

Itraconazole Capsules 100 mg 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:** For oral administration and must be taken immediately after a meal for maximal absorption.

### 4.3 Contraindications

Itraconazole capsules are contraindicated in patients with known hypersensitivity to itraconazole or to any of the excipients listed in formulation.

- Co-administration of a number of CYP3A4 substrates is contraindicated with itraconazole capsules. Increased plasma concentrations of these drugs, caused by coadministration with itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia.
- Itraconazole capsules 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.
- Itraconazole capsules must not be used during pregnancy (except for life-threatening cases).
- 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.

### 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<sub>2</sub>-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. 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, 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.

#### 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, pimozone, 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.

## **4.6 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

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 exanthematous 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	
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#### 4.9 Overdose

No data are available.

In the event 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 Pharmacodynamics properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.

ATC code: J02AC02

##### Mechanism of action

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

##### Pharmacokinetic/pharmacodynamic relationship

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

##### 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  $\leq 0.125$   $\mu\text{g/mL}$ , susceptible, dose-dependent 0.25-0.5 mg/mL and resistant  $\geq 1$   $\mu\text{g/mL}$ . Interpretive breakpoints have not been established for the filamentous fungi.

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<sub>90</sub> < 1mg itraconazole/L. There is no correlation between in vitro susceptibility and clinical efficacy.

Commonly susceptible species
<i>Aspergillus</i> spp.2
<i>Blastomyces dermatitidis</i> 1
<i>Candida albicans</i>
<i>Candida parapsilosis</i>

Cladosporium spp.
Coccidioides immitis <sup>1</sup>
Cryptococcus neoformans
Epidermophyton floccosum
Fonsecaea spp. 1
Geotrichum spp.
Histoplasma spp.
Malassezia (formerly Pityrosporum) spp.
Microsporum spp.
Paracoccidioides brasiliensis <sup>1</sup>
Penicillium marneffei <sup>1</sup>
Pseudallescheria boydii
Sporothrix schenckii
Trichophyton spp.
Trichosporon spp.
Species for which acquired resistance may be a problem
Candida glabrata <sup>3</sup>
Candida krusei
Candida tropicalis <sup>3</sup>
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

### 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.

### **Special Populations**

#### **Hepatic impairment:**

Itraconazole is predominantly metabolised in the liver. A pharmacokinetic study using a single 100 mg dose of itraconazole (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. A statistically significant reduction in average C<sub>max</sub> (47%) and a two fold increase in the elimination half-life ( $37 \pm 17$  versus  $16 \pm 5$  hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC, was similar in cirrhotic patients and in healthy subjects.

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

#### **Renal impairment:**

Limited data are available on the use of oral itraconazole in patients with renal impairment.

A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 ml/min.  $\times 1.73 \text{ m}^2$ , the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T<sub>max</sub>, C<sub>max</sub>, and AUC<sub>0-8h</sub>). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50-79 ml/min), moderate (defined in this study as CrCl 20-49 ml/min), and severe renal impairment (defined in this study as CrCl <20 ml/min) were similar to that in healthy subjects, (range of means 42-49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively.) Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole.

### **Paediatric Population**

Limited pharmacokinetic data are available on the use of itraconazole in the paediatric population. Clinical pharmacokinetic studies in children and adolescents aged between 5 months and 17 years were performed with itraconazole capsules, oral solution or intravenous formulation. Individual doses with the capsule and oral solution formulation ranged from 1.5 to 12.5 mg/kg/day, given as once-daily or twice-daily administration. The intravenous formulation was given either as a 2.5 mg/kg single infusion, or a 2.5 mg/kg infusion given once daily or twice daily. For the same daily dose, twice daily dosing compared to single daily dosing yielded peak and trough concentrations comparable to adult single daily dosing. No significant age dependence was observed for itraconazole AUC and total body clearance, while weak associations between age and itraconazole distribution volume, C<sub>max</sub> and terminal elimination rate were noted. Itraconazole apparent clearance and distribution volume seemed to be related to weight.

### 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

Sr. No.	Ingredients	Specification
1.	Hypromellose	USP
2.	Eudragit E-100	BP
3.	Sucrose Spheres	BP
4.	Macrogol 20000	BP
5.	Methylene Chloride	BP
6.	Ethanol	BP

### Composition of Black Edible Ink

Sr. No.	Ingredients	Quantity (%)
1.	Dewaxed Bleached Shellac Resins	18.90
2.	Isopropyl Alcohol	59.10
3.	Propylene Glycol	7.50
4.	Black Iron Oxide	13.70
5.	Sodium Lauryl Sulphate	0.80

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Store in a cool & dry place.

Keep out of reach of children.

### 6.5 Nature and contents of container <and special equipment for use, administration or implantation>

4 Capsules packed in Alu-PVC Blister. Such 1 blister is packed in a carton along with insert.

### 6.6 Special precautions for disposal <and other handling>

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MANUFACTURER****Yash Pharma Laboratories Pvt. Ltd.**

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