Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Candiforce-100 (Itraconazole 100 mg) Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains itraconazole 100 mg (as pellets)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gelatin white opaque capsules filled with off white to cream colored pellets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Vulvovaginal candidosis
2. Pityriasis versicolor
3. Dermatophytoses caused by organisms susceptible to itraconazole
4. Oral candidosis
5. Fungal keratitis
6. Systemic mycoses
7. Onychomycosis

4.2 Posology and method of administration

Candiforce is for oral administration and must be taken immediately after a meal for maximal absorption.
The capsulesmust be swallowed whole.
Treatment schedules in adults for each indication are as follows:

Short-Term Usage

Indication,	Dose
Vulvovaginal candidosis	200 mg twice daily for 1 day or 200 mg once daily for 3 days.
Pityriasis versicolor	200 mg once daily for 7 days
Tinea corporis, tinea cruris	100 mg once daily for 2 weeks or 200 mg once daily for 7 days
Tinea pedis, tinea manuum	100 mg once daily for 4 weeks
Oral candidosis	100 mg once daily for 2 weeks
Fungal keratitis	200 mg once daily for 3 weeks Treatment should not exceed 4 weeks.

Long Term Usage

Dosage recommendations vary according to the infection treated.

Indication,	Dose,	Median Duration
Onychomycosis,	200 mg od,	3 months
Aspergillosis,	200 mg od,	2-5 months
Candidosis,	100-200 mg od,	3 weeks - 7 months
Non-meningeal cryptococcosis,	200 mg od,	1-6 months
Cryptococcal meningitis,	200 mg bid,	2 months - 1 year
Histoplasmosis,	200 mg od - 200 mg bid,	8 months
Sporotrichosis	100 mg od,	3 months,
Paracoccidioidomycosis,	100 mg od,	6 months
Chromomycosis,	100-200 mg od,	6 months
Blastomycosis,	100 mg od - 200 mg bid,	6 months

Use in Children (below 12 years):
Clinical data on the use of Candiforce capsules in pediatric patients are limited. Candiforce capsules should not be used inchildren unless the potential benefit outweighs the potential risks. See 4.4 Special warnings and special precautions foruse.

Use in Elderly:
As for use in children

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

Use in patients with hepatic impairment:

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should beexercised when this drug is administered in this patient population. (See 5.2 Pharmacokinetic properties, Specialpopulations, Hepatic impairment).

4.3 Contraindications

Candiforce is also contra-indicated in patients who have shown hypersensitivity to the drug or to any of its excipients.Co-administration of the following drugs is contraindicated with Candiforce capsules *(see also 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 terfanadine are contraindicated with Candiforce capsules. Co-administration may result in increased plasma concentrations of these substrates, whichcan lead to QT prolongation and rare occurrences of torsades de pointes
- CYP3A4 metabolised HMG-CoA reductase inhibitors such as lovastatin and simvastatin
- Triazolam and oral midazolam
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine(methylergonovine)
- Eletriptan
- Nisoldipine

Candiforce capsules should not be administered to patients with evidence of ventricular dysfunction such as congestiveheart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections. See section 4.4

Candiforce must not be used during pregnancy (except for life-threatening cases). See section 4.6
Women of childbearing potential taking Candiforce should use contraceptive precautions. Effective contraception shouldbe continued until the menstrual period following the end of Candiforce therapy.

4.4 Special warnings and precautions for use

Cardiac effects
In a healthy volunteer study with Candiforce IV, a transient asymptomatic decrease of the left ventricular ejectionfraction was observed; this resolved before the next infusion. The clinical relevance of these findings to the oralformulations is unknown.

Itraconazole has been shown to have a negative inotropic effect and Candiforce has been associated with reports of CHF.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. Candiforce should not be used in patients with CHF or with a history of CHF 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 CHF. These risk factors include cardiac disease, such as ischaemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other oedematous disorders. Such patients should be informed of the signs and symptomsof CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment; if such signs or symptoms do occur during treatment,

Candiforce 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 used whenco-administering itraconazole and calcium channel blockers due to an increased risk of CHF (see Section 4.5, Interactions with other medicinal products).

Interaction potential
Candiforce has a potential for clinically important drug interactions. (See 4.5: Interaction with other medicinal productsand other forms of interaction).

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

Use in children
Clinical data on the use of Candiforce capsules in pediatric patients is limited. Candiforce capsules should not be used inpediatric patients unless the potential benefit outweighs the potential risks.

Hepatic effects
Liver function monitoring should be considered in patients receiving Candiforce treatment. Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Candiforce. Most of thesecases 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 have been observed within the first month of treatment, including some within the first week. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such asanorexia, 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 liver enzyme monitoring is necessary.

Hepatic impairment
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should beexercised when the drug is administered in this patient population. (See 5.2 Pharmacokinetic properties, Specialpopulations, Hepatic impairment).

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

Patients with immediately life-threatening systemic fungal infections
Due to the pharmacokinetic properties (see section 5.2), Candiforce capsules are not recommended for initiation oftreatment 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.

Neuropathy
If neuropathy occurs that may be attributable to Candiforce, treatment should be discontinued.

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

Cross Hypersensitivity
There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents.Caution should be used in prescribing Candiforce to patients wit hypersensitivity to other azoles.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltaseinsufficiency should not take this medicine.

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 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction, 3.Effect of itraconazole on the metabolism of other drugs). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

4.5 Interaction with other medicinal products and other forms of interaction

1. Drugs affecting the absorption of itraconazole:
Drugs that reduce the gastric acidity impair the absorption of itraconazole from Candiforce capsules (see 4.4 Specialwarnings and precautions for use).

2. Drugs affecting the metabolism of itraconazole:
Itraconazole is mainly metabolised through cytochrome CYP3A4. 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 dataare 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 thebioavailability of itraconazole.

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

3.1. Itraconazole can inhibit the metabolism of drugs metabolised 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 Section 5.2). This should be taken into account when the inhibitory effect of itraconazole on co-administered drugs is considered.

Examples are:

The following drugs are contraindicated with itraconazole:

- Astemizole, bepridil, cisapride, dofetilide, levamethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with Candiforce since co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsadesde pointes
- CYP3A4 metabolised HMG-CoA reductase inhibitors such as lovastatin and simvastatin
- Triazolam and oral midazolam
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotmaine and methylergometrine(methylergonovine).
- Nisoldipine

Caution should be used when co-administering itraconazole with calcium channel blockers due to an increased risk ofcongestive heart failure. IN addition to possible pharmacokinetic interactions involving the drug metabolizing enzymeCYP3A4, calcium channel blockers can have 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 bemonitored.

Their dosage, if co-administered with itraconazole, should be reduced if necessary:

- Oral anticoagulants;
- HIV protease inhibitors such as ritonavir, indinavir, saquinavir;
- Certain antineoplastic agents such as vinca alkaloids, busulphan, docetaxel and trimetrexate;
- CYP3A4 metabolised calcium channel blockers such as dihydropyridines and verapamil;
- Certain immunosuppressive agents: ciclosporin, tacrolimus, rapamycin (also known as sirolimus);
- Certain CY3A4 metabolised HMG-CoA reductase inhibitors such as atorvastatin;
- Certain glucocorticosteroids such as budesonide, dexamethasone, methylprednisolone and fluticasone;
- Digoxin (via inhibition of P-glycoprotein);
- Others: carbamazepine, cilostazol, buspirone, alfentanil, alprazolam, brotizolam, midazolam IV, disopyramide,eletriptan, fentanyl, halofantrine, rifabutin, repaglinide, ebastine, reboxetine.

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

4. 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, indomethacin, tolbutamide or sulfamethazine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Candiforce must not be used during pregnancy except for life-threatening cases where the potential benefit to the motheroutweighs the potential harm to the foetus (See section 4.3).

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

There is limited information on the use of Candiforce 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 Candiforcehas not been established.

Epidemiological data on exposure to Candiforce during the first trimester of pregnancy – mostly in patients receivingshort-term treatment for vulvovaginal candidosis – did not show an increased risk for malformations as compared tocontrol subjects no exposed to any known teratogens.

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

Lactation
A very small amount of itraconazole is excreted in human milk. The expected benefits of Candiforce therapy should beweighed against the risks of breast feeding. In case of doubt, the patient should not breast feed.

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 (seeSection 4.8), which may occur in some instances, must be taken into account.

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) with Candiforce Capsules treatment identified from clinical trials and/or from spontaneous reporting were headache, abdominal pain, and nausea. The most serious ADRs were serious allergic reactions, cardiac failure/congestive heart failure/pulmonary oedema, pancreatitis, serious hepatotoxicity (including some cases of fatal acute liver failure), and serious skin reactions.

The table below presents ADRs by System Organ Class. Within each System Organ Class, the ADRs 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).

Adverse Drug Reactions	
Infections and infestations	
Uncommon	Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and lymphatic system disorders	
Rare	Leukopenia
Immune system disorders	
Uncommon	Hypersensitivity*
Rare	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Metabolism and nutrition disorders	
Rare	Hypertriglyceridaemia
Nervous system disorders	

Adverse Drug Reactions	
Common	Headache
Rare	Paraesthesia, Hypoaesthesia, Dysgeusia
Eye disorders	
Rare	Visual disturbance (including diplopia and blurred vision)
Ear and labyrinth disorder	
Rare	Transient or permanent hearing loss*, Tinnitus
Cardiac disorders	
Rare	Congestive heart failure*
Respiratory, thoracic and mediastinal disorders	
Rare	Dyspnoea
Gastrointestinal disorders	
Common	Abdominal pain, Nausea
Uncommon	Diarrhoea, Vomiting, Constipation, Dyspepsia, Flatulence
Rare	Pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic function abnormal
Rare	Serious hepatotoxicity (including some cases of fatal acute liver failure)*, Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, Rash, Pruritus
Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Renal and urinary disorders	
Rare	Pollakiuria
Reproductive system and breast disorders	
Uncommon	Menstrual disorder
Rare	Erectile dysfunction
General disorders and administration site conditions	
Rare	Oedema
Investigations	
Rare	Blood creatine phosphokinase increased

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 removedby haemodialysis.
No specific antidote is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Antimycotic for systemic use, triazole derivatives
ATC code: J02A C02

Itraconazole, a triazole derivative, has a broad spectrum of activity.
In vitro studies have demonstrated that itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is avital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.

For itraconazole, breakpoints have only been established for Candida spp. from superficial mycotic infections (CLSIM27-A2, breakpoints have not been established for EUCAST methodology). The CLSI breakpoints are as follows: susceptible <0.125; susceptible, dose-dependent 0.25-0.5 and resistant >1 0g/mL. Interpretive breakpoints have not been established for the filamentous fungi.

In vitro studies demonstrate that itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually 1 µg/ml. These include: dermatophytes (Trichophyton spp., Microsporum spp., Epidermophyton floccosum); yeasts (Candida spp., including C. albicans, Cryptococcus neoformans, Malassezia spp., Trichosporon spp., Geotrichum spp.); Aspergillus spp.; Histoplasma spp.; Paracoccidioides brasiliensis; Sporothrix schenckii; Fonsecaea spp.; Cladosporium spp.; Blastomyces dermatitidis; Coccidioides immitis; Pseudallescheria boydii;Penicillium marneffei; and various other yeasts and fungi.

Candida krusei, Candida glabrata and Candida tropicalis are generally the least susceptible Candida species, with someisolates showing unequivocal resistance to itraconazole in vitro.

The principal fungus types that are not inhibited by itraconazole are Zygomycetes (e.g. Rhizopus spp., Rhizomucorspp., Mucor spp. and Absidia spp.), Fusarium spp., Scedosporium spp. and Scopulariopsis spp.

Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14a-demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux. Cross- resistance between members of the azole class has been observed within Candida spp., although resistance to one member of the class does not necessarily confer resistance to other azoles. Itraconazole-resistant strains of Aspergillusfumigatus have been reported.

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. In general, itraconazole is well absorbed. Peak plasma concentrations are reached within 2to 5 hours following administration of the oral solution.

Itraconazole undergoes extensive hepatic metabolism to give numerous metabolites. The main metabolite is hydroxy-itraconazole, with plasma concentrations about twice those of the unchanged drug. The terminal half-life of itraconazole is about 40 hours after repeated dosing.
The pharmacokinetics of itraconazole is characterised by non-linearity and, consequently, shows accumulation in plasma after multiple dose administration. Steady-state concentrations are reached within 15 days, with C_{max} values ofabout 2 µg/ml after oral administration of 200 mg once daily. Itraconazole clearance decreases at higher doses due to a saturable mechanism of its hepatic

metabolism. Itraconazole is excreted as inactive metabolites in urine (~35%) and infaeces (~54%).

Absorption:
Itraconazole is rapidly absorbed after administration of the oral solution. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral dose. The observed absolute bioavailability of itraconazole underfed conditions 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 ispresent 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 thancorresponding concentrations in plasma. Brain to plasma ratios were about 1.

The uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma.

Metabolism:
Itraconazole is extensively metabolised by the liver into a large number of metabolites. The main metabolite is hydroxy-itraconazole which has in vitro antifungal activity comparable to itraconazole. Plasma concentrations of thehydroxy-metabolite 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.

Excretion:
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.

As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeksafter discontinuation of a 4-week treatment and in nail keratin – where itraconazole can be detected as early as 1 week after start of treatment
– for at least six months after the end of a 3-month treatment period.

Special Populations
Hepatic impairment
Itraconazole is predominantly metabolised in the liver. A single oral dose (100 mg capsule) was administered to 12 patients with cirrhosis and six healthy control subjects; Cmax, AUC and terminal half-life of itraconazole were measured and compared between groups. Mean itraconazole Cmax was reduced significantly (by 47%) in patients withcirrhosis. Mean elimination half-life was prolonged compared to that found in subjects without hepatic impairment (37vs. 16 hours, respectively). 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. *(See sections 4.2 Posology and method of administration, and 4.4 Special warnings and special precautions for use.)*

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

5.3 Preclinical safety data

Itraconazole:
Itraconazole has been tested in a standard battery of non-clinical safety studies.
Acute toxicity studies with itraconazole in mice, rats, guinea pigs and dogs indicate a wide safety margin. Sub (chronic)oral toxicity studies in rats and dogs revealed several target organs or tissues: adrenal cortex, liver and mononuclear phagocyte system as well as disorders of the lipid metabolism presenting as xanthoma cells in various organs.

At high doses, histological investigations of adrenal cortex showed a reversible swelling with cellular hypertrophy ofthe zona reticularis and fasciculata, which was sometimes associated with a thinning of the zona glomerulosa.
Reversible hepatic changes were found at high doses. Slight changes were observed in the sinusoidal cells and vacuolation of the hepatocytes, the latter indicating cellular dysfunction, but without visible hepatitis or hepatocellularnecrosis.

Histological changes of the mononuclear phagosystem were mainly characterised by macrophages with increasedproteinaceous material in various parenchymal tissues.

There are no indications of a mutagenic potential of itraconazole. Itraconazole is not a primary carcinogen in rats or mice. In male rats, however, there was a higher incidence of soft-tissue sarcoma, which is attributed to the increase innon-neoplastic, chronic inflammatory reactions of the connective tissue as a consequence of raised cholesterol levels and cholesterosis in connective tissue.

There is no evidence of a primary influence on fertility under treatment with itraconazole. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats and mice at high doses. Inrats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and macroglossia.
A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration.

In three toxicology studies using rats, itraconazole induced bone defects. The induced defects included reduced boneplate activity, thinning of the zona compacta of the large bones, and increased bone fragility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres
Hypromellose 2910 5mPa.s
Macrogol 20000

Capsule shell:
Titanium dioxide
Indigo carmine
Gelatin
Erythrosine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on themarket in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

3 Blisters of 10 Capsules packed in Alu/PVC are packed in a carton

6.6 Special precautions for disposal of a used medicinal product or waste materials derived fromsuch medicinal product and other handling of the product

No special requirements.

7 PRODUCT AUTHORISATION HOLDER

Mankind Pharma Limited
208, Okhla Industrial Estate,
Phase III, New Delhi – 20
INDIA

8 PRODUCT AUTHORISATION NUMBER

TAN 20 HM 0130

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

July 09, 2020

10. DATE OF REVISION OF THE TEXT
October 13, 2023