Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sporanox 100mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains itraconazole 100 mg.
Excipient: Contains Sucrose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Imported from Greece:
Sporanox capsules have an opaque blue cap and pink transparent body containing coated beads.

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

Sporanox is for oral administration and must be taken immediately after a meal for maximal absorption. The capsules must 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 Sporanox capsules in pediatric patients are limited. Sporanox capsules should not be used in children unless the potential benefit outweighs the potential risks. See 4.4 Special warnings and special precautions for use.

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 be exercised 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. Itraconazole is predominantly metabolised in the liver. The terminal half-life of itraconazole in cirrhotic patients is somewhat prolonged. Caution should be exercised when this drug is administered in this patient population. (See 5.2 Pharmacokinetic properties, Special populations, Hepatic impairment.

4.3 Contraindications

Sporanox 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 Sporanox capsules (see also section 4.5 Interaction with other medicinal products and other forms of interaction):
• 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 Sporanox capsules. 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

• Triazolam and oral midazolam

• Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)

• Nisoldipine

Sporanox 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. See 4.4 Special warnings and precautions for use.
Sporanox must not be used during pregnancy (except for life-threatening cases). See section 4.6 Pregnancy and lactation.

4.4 Special warnings and precautions for use

Cardiac effects
In a healthy volunteer study with Sporanox™ IV, 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 Sporanox 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.

Sporanox 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 symptoms of 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, Sporanox 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 when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF (see Section 4.5, Interactions with other medicinal products).

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

Reduced gastric acidity
Absorption of itraconazole from Sporanox is impaired when gastric acidity is decreased. In patients also receiving acid neutralising medicines (eg aluminium hydroxide), these should be administered at least 2 hours after the intake of Sporanox. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (eg H2-antagonists, proton pump inhibitors), it is advisable to administer Sporanox with a cola beverage.

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

Hepatic effects
Liver function monitoring should be considered in patients receiving Sporanox treatment. Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Sporanox. 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 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 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 liver enzyme monitoring is necessary.

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 Pharmacokinetic properties, Special populations, Hepatic impairment)

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

Patients with immediately life-threatening systemic fungal infections
Due to the pharmacokinetic properties (see section 5.2), Sporanox capsules are not recommended for initiation of treatment 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 Sporanox, treatment should be discontinued.

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.

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

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 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

4.5.1. Drugs affecting the absorption of itraconazole:
Drugs that reduce the gastric acidity impair the absorption of itraconazole from Sporanox capsules (see 4.4 Special warnings and precautions for use).

4.5.2. 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 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.

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

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 5.2 Pharmacokinetic Properties). 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, setindole and terfenadine are contraindicated with Sporanox 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

• Triazolam and oral midazolam

• Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotmaine and methylergometrine (methylergonovine).

• Nisoldipine

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF..

Drugs whose plasma levels, effects or side effects should be monitored. Their dosage, when 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 and 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.

2. 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.

4.5.4. 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 sulphadimidine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Sporanox 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 Contraindications).

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

There is limited information on the use of Sporanox 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 Sporanox has not been established.

Epidemiological data on exposure to Sporanox 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 no exposed to any known teratogens.

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

Lactation
A very small amount of itraconazole is excreted in human milk. The expected benefits of Sporanox therapy should be weighed 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

None known.

4.8 Undesirable effects

In double-blind, controlled clinical trials involving 2104 itraconazole-treated patients in the treatment of dermatomycoses or onychomycosis, the most frequently reported adverse experiences in clinical trials 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 category, 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).

Adverse Drug Reactions	
Blood and lymphatic system disorders	
Rare	Leukopenia
Not known	Neutropenia, Thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity
Not known	Serum Sickness, Angioneurotic Oedema, Anaphylactic Reaction, Anaphylactoid Reaction
Metabolism and nutrition disorders	
Not known	Hypertriglyceridaemia, Hypokalemia
Nervous system disorders	
Uncommon	Headache, Dizziness, Paraesthesia.
Rare	Hypoaesthesia

Not known	Peripheral Neuropathy
Eye disorders	
Rare	Visual Disturbance
Not known	Vision Blurred and Diplopia
Ear and labyrinth disorder	
Rare	Tinnitus
Not known	Transient or permanent hearing loss
Cardiac disorders	
Not known	Congestive Heart Failure
Respiratory, thoracic and mediastinal disorders	
Not known	Pulmonary Oedema
Gastrointestinal disorders	
Common	Abdominal pain, Nausea.
Uncommon	Vomiting, Diarrhoea, Constipation, Dyspepsia, Dysgeusia, Flatulence
Rare	Pancreatitis
Hepato-biliary disorders	
Uncommon	Hyperbilirubinaemia, Alanine Aminotransferase Increased. Aspartate Aminotranferase Increased
Rare	Hepatic Enzyme Increased
Not known	Fatal Acute Hepatic Failure, Hepatitis, Hepatotoxicity
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Urticeria, Alopecia, Pruritus
Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Photosensitivity
Musculosketal and connective tissue disorders	
Not known	Myalgia, Arthralgia
Renal and urinary disorders	
Rare	Pollakiuria
Not known	Urinary incontinence
Reproductive system and breast disorders	
Uncommon	Menstrual disorders
Not known	Erectile dysfunction
General disorders and administration site conditions	
Uncommon	Oedema
Rare	Pyrexia

4.9 Overdose

In the event of an overdose, 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 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 or ergosterol in fungal cells. Ergosterol is a vital 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 (CLSI M27-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 >10g/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 some isolates showing unequivocal resistance to itraconazole *in vitro*.

The principal fungus types that are not inhibited by itraconazole are *Zygomycetes* (e.g. *Rhizopus spp*., *Rhizomucor spp*., *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 14α-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 *Aspergillus fumigatus* 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 2.5 hours following administration of the oral solution. Itraconazole undergoes extensive hepatic metabolism to give numerous metabolites. The main metabolite is hydroxyitraconazole, 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 nonlinearity and, consequently, shows accumulation in plasma after multiple dose administration. Steady-state concentrations are reached within 15 days, with C_{max} values of about 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 in faeces (~54%).
Absorption:
Itraconazole is rapidly absorbed after administration of the oral solution. Peak plasma concentrations of the unchanged drug are reached within 2.5 hours following an oral dose. The observed absolute bioavailability of itraconazole under fed 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 hydroxymetabolite). 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.

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 hydroxyitraconazole which has *in vitro* antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxymetabolite 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 weeks after 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 with cirrhosis. Mean elimination half-life was prolonged compared to that found in subjects without hepatic impairment (37 vs. 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 be exercised when the drug is administered in this patient population.

5.3 Preclinical safety data

Itraconazole:
Itraconazole has been tested in a standard battery of nonclinical 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 of the 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 hepatocellular necrosis. Histological changes of the mononuclear phagosystem were mainly characterised by macrophages with increased proteinaceous 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 in non-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. In rats, 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 bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose spheres
Hypromellose
Macrogol
Titanium dioxide (E171)
Indigotine
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 blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C .
Store in the original package.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

Blister strip in packs of 15 capsules.

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

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing Limited,
Ballymurray,
Co. Roscommon,
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1447/22/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23rd May 2008

10 DATE OF REVISION OF THE TEXT

September 2010