Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sporanox 100mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains itraconazole 100 mg.

Also contains sucrose.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Product imported from Greece:
Gelatin capsule with 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 four 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

Impaired absorption in AIDS and neutropenic patients may lead to low intraconazole blood levels and lack of efficacy. In such cases, blood level monitoring is indicated.

Use in children (below 12 years): There are inadequate data on Sporanox in children for its use to be recommended, unless the potential benefits outweigh the risks. See section 4.4 Special Warnings and Precautions for Use.

In Elderly: As for use in children.

Use in patients with renal impairment: The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. A dose adjustment may be considered (see special warnings and precautions for use).

Use in patients with hepatic impairment: Itraconazole is predominantly metabolised in the liver. The terminal half-life of itraconazole in cirrhotic patients is somewhat prolonged. The oral bioavailability in cirrhotic patients is somewhat decreased. A dose adjustment may be considered (see special warnings and precautions for use).

4.3 Contraindications

Sporanox is also contra-indicated in patients who have shown hypersensitivity to the drug or 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, 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).

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.
Itraconazole has been shown to have a negative inotropic effect and SPORANOX has been associated with reports of congestive heart failure. SPORANOX 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, and individual risk factors for congestive heart failure. 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 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, SPORANOX should be discontinued. 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 (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 H_2-antagonists, proton pump inhibitors), it is advisable to administer SPORANOX with a cola beverage.

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
Itraconazole is predominantly metabolised in the liver. The terminal half-life of itraconazole in cirrhotic patients was significantly increased. The oral bioavailability in cirrhotic patients is somewhat decreased. A dose adjustment should be adapted if necessary.

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
The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. A dose adjustment may be considered.

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.

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

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 Sporanox capsules (see 4.4 Special warnings 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 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.

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

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.

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;
- Others: digoxin, carbamazepine, cilostazol, buspirone, alfentanil, alprazolam, brotizolam, midazolam IV, disopyramide, eletriptan, 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.

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

Clinical trials
The table below shows the adverse events reported among patients in placebo-controlled trials (pooled data) of Sporanox capsules, in the treatment of dermatomycosis and onychomycosis. It includes all adverse events (with an

incidence of 1% or greater) reported among Sporanox-treated patients. About 28% of patients treated with Sporanox capsules and about 23% of patients treated with placebo experienced at least one adverse event. The adverse events reported are summarized irrespective of the causality assessment of the investigators.
The most frequently reported adverse events in clinical trials were of gastrointestinal origin.
Table: Adverse events reported among Sporanox-treated patients with an incidence of ≥1%.

	Sporanox N=929 %	Placebo N=661 %
Body as a whole	**5.8**	**5.9**
Injury	2.9	3.0
Central and peripheral nervous system disorders	**5.7**	**6.4**
Headache	4.0	5.0
Gastrointestinal disorders	**9.0**	**6.5**
Nausea	2.4	2.6
Diarrhoea	2.3	2.0
Abdominal pain	1.8	1.4
Dyspepsia	1.7	0.9
Flatulence	1.3	0.5
Liver and biliary system disorders	**2.2**	**1.1**
Hepatic function abnormal	1.0	0.3
Respiratory system disorders	**6.0**	**5.7**
Rhinitis	2.0	2.1
Upper respiratory tract infection	1.8	1.1
Sinusitus	1.7	1.2
Skin and Appendages Disorders	**5.1**	**2.1**
Rash	2.5	0.6

Post-marketing experience:
Within each system organ class, the adverse drug reactions are ranked under the headings of reporting frequency, using the following convention:
Very common > 1/10)
Common > 1/100, < 1/10)
Uncommon > 1/1000, < 1/100)
Rare > 1/10000, < 1/1000)
Very rare (< 1/10000) including isolated reports.
The reporting frequency of the adverse drug reactions is based upon the post - marketing experience across all three Sporanoxformulations: Sporanox capsules, Sporanox liquid and Sporanox I.V.

Immune system disorders
Very rare: anaphylactic, anaphylactoid and allergic reactions

Metabolism and Nutrition Disorders
Very rare: *hypokalemia*

Nervous System Disorders
Very rare: peripheral neuropathy, headache, and dizziness

Cardiac Disorders
Very rare:congestive heart failure

Respiratory, Thoracic and Mediastinal Disorders

Very rare:pulmonary oedema

Gastrointestinal Disorders
Very rare:abdominal pain, vomiting, dyspepsia, nausea, diarrhoea and constipation

Hepato-Biliary Disorders
Very rare:serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, and reversible increases in hepatic enzymes

Skin and Subcutaneous Tissue Disorders
Very rare:Stevens-Johnson syndrome, angio-oedema, urticaria, alopecia, photosensitivity, rash, and pruritis

Reproductive System and Breast Disorders
Very rare:menstrual disorder

General Disorders and Administrative Site Conditions
Very rare:oedema

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 demonstrate that itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually ranging from ≤0.025-0.8 µg/ml. These include:

Dermatophytes (*Trichophyton spp*., *Microsporum spp*., *Epidermophyton floccosum*); yeasts (*Candida spp*., including *C. albicans, C. glabrata* and *C. krusei, Cryptococcus neoformans, Pityrosporum spp., Trichosporon spp., Geotrichum spp*.); *Aspergillus spp*.; *Histoplasma spp*.; *Paracoccidioides brasiliensis*; *Sporothrix schenckii*; *Fonsecaea spp*.; *Cladosporium spp*.; *Blastomyces dermatitidis*; *Pseudallescheria boydii*; *Penicillium marneffei*; and various other yeasts and fungi.

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*

In vitro studies have demonstrated that itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is a vital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.

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 hydroxyl-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 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% and increases by 30% when the oral solution is taken in fasting conditions.

Distribution:
Most of the itraconazole in plasma is bound to protein (99.8%) with albumin being the main binding component (99.6% for the hydroxyl-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.
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 hydroxyl-itraconazole which has *in vitro* antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxyl-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.

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 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
Gelatin
Titanium dioxide
Indigotine (E132)
Erythrosine (E127)

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 the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister pack of 15 capsules contained in an over-labelled outer cardboard carton.

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

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
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Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/137/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 2004
Date of last renewal: 26 November 2009

10 DATE OF REVISION OF THE TEXT

August 2011