SPORANOX®

DATA SHEET

NAME OF THE MEDICINE

SPORANOX™ itraconazole 10 mg/mL oral solution

PRESENTATION

SPORANOX 10 mg/mL oral solution (150 mL) is supplied in amber glass bottles with a child-resistant cap.

USES

Actions

Itraconazole is a synthetic triazole derivative. When administered orally, it has shown fungistatic activity against superficial dermatophytes and *Candida* species including *C. albicans and C. glabrata.*
Itraconazole has shown *in vitro* antifungal activity against a variety of fungi and yeasts. This spectrum includes superficial dermatophytes (*Trichophyton* spp*., Microsporum* spp*., Epidermophyton floccosum*), yeasts (*Cryptococcus neoformans, Pityrosporum* spp*., Candida* spp. including *C. albicans*, *C. glabrata* and *C. krusei*), *Aspergillus* spp., *Histoplasma* spp., *Paracoccidioides brasiliensis, Sporothrix schenckii*, *Fonsecaea* spp., *Cladosporium* spp., *Blastomyces dermatitidis*.
In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Pharmacokinetics

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with C_{max} values of 0.5 µg/ml, 1.1 µg/ml and 2.0 µg/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

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 capsule dose. The observed

absolute oral bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H_2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see **WARNINGS AND PRECAUTIONS**, and **INTERACTIONS** section). Absorption of itraconazole under fasted conditions in these subjects is increased when SPORANOX capsules are administered with an acidic beverage (such as a non-diet cola). When SPORANOX capsules were administered as a single 200-mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H_2-receptor antagonist, itraconazole absorption was comparable to that observed when SPORANOX capsules were administered alone (see **INTERACTIONS** section.)

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given (see **WARNINGS AND PRECAUTIONS** section.)

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 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, and the uptake into keratinous tissues, skin in particular, up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

Metabolism

Itraconazole is extensively metabolized by the liver into a large number of metabolites. *In vitro* studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole; trough plasma concentrations of this metabolite are about twice those of itraconazole.

Excretion

Itraconazole is excreted mainly as inactive metabolites in urine (35%) and in feces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabeled dose, fecal excretion of unchanged drug ranges from 3% to 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 metabolized in the liver. A pharmacokinetic study was conducted in 6 healthy and 12 cirrhotic subjects who were administered a single 100-mg dose of itraconazole as a capsule. A statistically significant reduction in mean C_{max} (47%) and a twofold increase in the elimination half-life (37 ± 17 hours vs. 16 ± 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. See **DOSAGE AND ADMINISTRATION** and **WARNING AND PRECAUTIONS** section.

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. × 1.73 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_{max}, C_{max}, and AUC_{0-8h}). 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. See also **DOSAGE AND ADMINISTRATION** and **WARNING AND PRECAUTIONS** section.

Paediatrics

Limited pharmacokinetic data are available on the use of itraconazole in the pediatric 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_{max} and terminal elimination

rate were noted. Itraconazole apparent clearance and distribution volume seemed to be related to weight.

Hydroxypropyl-ß-Cyclodextrin

The oral bioavailability of hydroxypropyl-β-cyclodextrin given as a solubilizer of itraconazole in oral solution is on average lower than 0.5% and is similar to that of hydroxypropyl-β-cyclodextrin alone. This low oral bioavailability of hydroxypropyl-β-cyclodextrin is not modified by the presence of food and is similar after single and repeated administrations.

INDICATIONS

SPORANOX oral solution is indicated for the:

- treatment of oral and/or oesophageal candidiasis in HIV-positive or other immunocompromised patients.
- prophylaxis of fungal infections in neutropenic patients.

DOSAGE AND ADMINISTRATION

For optimal absorption, SPORANOX oral solution should be taken without food. The solution should be swished in the oral cavity and swallowed. There should be no rinsing after swallowing.
Treatment of oral and/or oesophageal candidiasis: 200 mg (2 measuring cups or 20 mL) once a day or 100 mg (1 measuring cup or 10 mL) twice a day for 1 week. If there is no response after 1 week, treatment should be continued for another week.
Treatment of fluconazole-resistant oral and/or oesophageal candidiasis: 200 to 400 mg (2-4 measuring cups or 20-40 mL) daily in one or two intakes for 2 weeks. If there is no response after 2 weeks, treatment should be continued for another 2 weeks.
Prophylaxis of fungal infections: 5 mg/kg per day administered as a twice daily dose until recovery of neutrophils. In clinical trials, prophylaxis treatment was started immediately prior to the cytostatic treatment and generally one week before transplant procedure.
For use in children, the elderly and in patients with renal or hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Special Populations

Paediatrics

Clinical data on the use of SPORANOX oral solution in paediatric patients are limited. The use of SPORANOX oral solution in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks. See **WARNINGS AND PRECAUTIONS** section.
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. The incidence of adverse events such as diarrhoea, abdominal pain, vomiting, fever, rash and mucositis was higher in adults. However, it is not clear to what extent this is attributable to SPORANOX oral solution or chemotherapy.

Elderly

Clinical data on the use of SPORANOX oral solution in elderly patients are limited. It is advised to use SPORANOX oral solution in these patients only if it is determined that the potential

benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. See **WARNINGS AND PRECAUTIONS** section.

Hepatic impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. See **Pharmacokinetics** section.

Renal impairment

Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered.

CONTRAINDICATIONS

SPORANOX oral solution is contraindicated in patients who have shown hypersensitivity to itraconazole or the excipients.

SPORANOX oral solution should only be given to pregnant women in life-threatening cases and when in these cases the potential benefit outweighs the potential harm to the foetus. Adequate contraceptive precautions should be used by women of childbearing potential throughout SPORANOX therapy, and continued until the next menstrual period following the end of SPORANOX therapy.

Coadministration of a number of CYP3A4 substrates is contraindicated with SPORANOX oral solution. 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 tachyarrythmias including, occurrences of torsades de pointes, a potentially fatal arrhythmia. Specific examples are listed in **INTERACTIONS** section.

SPORANOX oral solution 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 **WARNING AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

SPORANOX has a potential for clinically important interactions with other medicines (see **INTERACTIONS**).

Congestive heart failure

In a study with SPORANOX IV in healthy volunteers a transient asymptomatic decrease of the left ventricular ejection fraction, which resolved before the next infusion, was observed. The clinical relevance of these findings to the oral formulations is not known.

Itraconazole has been shown to have a negative inotropic effect. SPORANOX 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.

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. The risk benefit

assessment should consider factors such as the severity of the indication, the dosing regimen (e.g. total daily dose) and individual risk factors for congestive heart failure. 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. Patients with these risk factors, who are being treated with SPORANOX, should be informed of the signs and symptoms of congestive heart failure. Caution should be exercised and the patient monitored for the signs and symptoms of congestive heart failure. SPORANOX should be discontinued if such symptoms occur during treatment.
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.

Interaction potential

Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death. Drugs that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in **INTERACTIONS.**

Cross-hypersensitivity

There is -limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX oral solution to patients with hypersensitivity to other azoles.

Cystic fibrosis

In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady state dosing of oral solution using 2.5 mg/kg twice daily. Steady state concentrations of $>$ 250 ng/mL were achieved in approximately 50% of subjects aged 16 years and older, but in none of the patients under 16 years of age. If a patient does not respond to SPORANOX oral solution, consideration should be given to switching to alternative therapy.
Treatment of severely neutropenic patients: SPORANOX oral solution as treatment for oral and/or oesophageal candidasis was not investigated in severely neutropenic patients. Due to the pharmacokinetic properties, SPORANOX oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidasis.

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 **CONTRAINDICATIONS** and **INTERACTIONS** section). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

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 it is recommended to have their sensitivity tested before the start of itraconazole therapy.

Interchangeability

It is not recommended that SPORANOX capsules and SPORANOX oral solution be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose is given.

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. Dose adjustments may be considered.
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. Liver function monitoring should be considered in patients receiving SPORANOX 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.
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. It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. It is recommended that the prolonged elimination of half-life itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolized by CYP3A4.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with SPORANOX is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. (See Pharmacokinetics section. Renal impairment)

Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered.

Peripheral neuropathy

Isolated cases of peripheral neuropathy have also been reported, predominantly during long-term treatment with SPORANOX. If neuropathy occurs that may be attributable to SPORANOX, the treatment should be discontinued.

Other azole antifungal agents

There is limited information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX oral solution to patients with hypersensitivity to other azoles.

Use in children

Since clinical data on the use of SPORANOX oral solution in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks.
Limited safety experience is available with a dose of 5 mg/kg per day. The incidence of adverse events such as diarrhoea, abdominal pain, vomiting, fever, rash and mucositis was higher than in adults.
Toxicological studies have shown that itraconazole, when administered to rats, can produce bone toxicity. While such toxicity has not been reported in adult patients, the long-term effect of itraconazole in children is unknown (See **FURTHER INFORMATION - Toxicology**).

Use in elderly patients

Clinical data on the use of SPORANOX oral solution in elderly patients is limited. Use SPORANOX oral solution in these patients only if the potential benefits outweigh the potential risks.

Pregnancy and lactation

Use in pregnancy

Category B3. Teratogenic effects: Itraconazole was found to cause a dosage-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day and in mice at dosage levels of approximately 80 mg/kg/day. In rats, the teratogenicity consisted of major skeletal defects and in mice it consisted of encephaloceles and/or macroglossia.
Itraconazole must not be used during pregnancy except for life-threatning cases where the potential benefit to the mother outweighs the potential harm to the foetus (see **CONTRAINDICATIONS**).
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 casual 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 candidiasis) did not show an increased risk of malformations as compared to control subjects not exposed to any known teratogens. Itraconazole has been shown to cross the placenta in a rat model.

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

Use in lactation

Based on the determination of itraconazole concentration in the breast milk of lactating mothers who received a single daily dose of 400 mg itraconazole (200 mg b.i.d.), it was calculated that the exposure in the infant to itraconazole would be around 450 times lower than in the mother. The expected benefits of SPORANOX therapy should therefore be weighed

against the potential risk of breast-feeding. In case of doubt the patient should not breast-feed.
FertilityRefer to **FURTHER INFORMATION – Carcinogenesis, mutagenicity, impairment of fertility** section for information relevant to itraconazole and hydroxyl-beta-cyclodextrin.

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 (See ADVERSE EFFECTS section). Adverse Effects
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of itraconazole based on the comprehensive assessment of the available adverse event information. A causal relationship with itraconazole cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data
The safety of SPORANOX oral solution was evaluated in 889 patients who participated in six double-blind and four open-label clinical trials. Of the 889 patients treated with SPORANOX oral solution, 624 patients were treated with SPORANOX oral solution during the double-blind trials. All 889 patients received at least one dose of SPORANOX oral solution for the treatment of oropharyngeal and esophageal candidiasis and provided safety data. Adverse drug reactions (ADRs) reported for ≥1% of patients treated with SPORANOX oral solution in these clinical trials are shown in Table 1.

Table 1	**Adverse Drug Reactions Reported by ≥1% of Patients Treated with SPORANOX Oral Solution in 10 Clinical Trials**
System Organ Class Adverse Drug Reaction	SPORANOX Oral Solution % (N=889)
Nervous System Disorders	
Headache	3.6
Dysgeusia	1.5
Dizziness	1.1
Respiratory, Thoracic and Mediastinal Disorders	
Cough	1.8
Gastrointestinal Disorders	
Diarrhoea	9.1
Nausea	8.2
Vomiting	5.2
Abdominal Pain	4.5
Dyspepsia	1.0
Skin and Subcutaneous Tissue Disorders	
Rash	2.5
General Disorders and Administration Site Conditions	
Pyrexia	5.2

Adverse drug reaction that occurred in <1% of patients treated with SPORANOX oral solution in these clinical trials are listed in Table 2.

Table 2	**Adverse Drug Reactions Reported by <1% of Patients Treated with SPORANOX Oral**

Solution in 10 Clinical Trials
System Organ Class Adverse Drug Reactions
Blood and Lymphatic System Disorders Leukopenia Thrombocytopenia
Immune System Disorders Hypersensitivity
Metabolism and Nutrition Disorders Hypoesthesia Neuropathy peripheral Paresthesia
Ear and Labyrinth Disorders Tinnitus
Cardiac Disorders Cardiac failure
Gastrointestinal Disorders Constipation
Hepatobiliary Disorders Hepatic failure Hyperbilirubinemia
Skin and Subcutaneous Tissue Disorders Pruritus Urticaria
Musculoskeletal and Connective Tissue Disorders Arthralgia Myalgia
Reproductive System and Breast Disorders Menstrual disorder
General Disorders and Administrative Site Conditions Oedema

The following is a list of additional ADRs associated with itraconazole that have been reported in clinical trials of SPORANOX capsules and SPORANOX IV, excluding the ADR term "Injection site inflammation" which is specific to the injection route of administration.
Infections and Infestations: Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and Lymphatic Disorders: Granulocytopenia
Immune System Disorders: Anaphylactoid reaction
Metabolism and Nutrition Disorders: Hyperglycemia, Hyperkalemia, Hypomagnesemia
Psychiatric Disorders: Confusional state
Nervous System Disorders: Somnolence, Tremor
Cardiac Disorders: Left ventricular failure, Tachycardia
Vascular Disorders: Hypertension, Hypotension
Respiratory, Thoracic and Mediastinal Disorders: Pulmonary edema, Dysphonia
Gastrointestinal Disorders: Gastrointestinal disorder, Flatulence
Hepatobiliary Disorders: Hepatitis, Jaundice, Hepatic function abnormal
Skin and Subcutaneous Tissue Disorders: Rash erythematous, Hyperhidrosis
Renal and Urinary Disorders: Renal impairment, Pollakiuria, Urinary incontinence
Reproductive System and Breast Disorders: Erectile dysfunction
General Disorders and Administration Site Conditions: Generalized edema, Face edema, Chest pain, Pain, Fatigue, Chills

Paediatrics
The safety of SPORANOX oral solution was evaluated in 250 paediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least

one dose of SPORANOX oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data.
Based on pooled safety data from these clinical trials, the very common reported ADRs in paediatric patients were Vomiting (36.0%), Pyrexia (30.8%), Diarrhoea (28.4%), Mucosal inflammation (23.2%), Rash (22.8%), Abdominal Pain (17.2%), Nausea (15.6%), Hypertension (14.0%), and Cough (11.2%). The nature of ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in paediatric patients.

Post-marketing data

Adverse drug reactions first identified during the post-marketing experience with SPORANOX (all formulations) are included in Table 3. In this table, the frequencies are provided according to the following convention:

Very common	(≥ 1/10)
Common	(≥1/100 and < 1/10)
Uncommon	(≥1/1,000 and < 1/100)
Rare	(≥1/10,000 and < 1/1000)
Very rare	(<1/10,000), including isolated reports.

Table 3:	**Adverse Reactions Identified During Post-Marketing Experience with SPORANOX by Frequency Category Estimated from Spontaneous Reporting Rates**
Immune System Disorders	
Very rare	*Serum sickness, Angioneurotic edema, Anaphylactic reaction*
Metabolism and Nutrition Disorders	
Very rare	Hypertriglyceridemia
Nervous System Disorders	
Very rare	Tremor
Eye Disorders	
Very rare	Visual disturbances (including diplopia and vision blurred)
Ear and Labyrinth Disorders	
Very rare	Transient or permanent hearing loss
Cardiac Disorders	
Very rare	Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Dyspnea
Gastrointestinal Disorders	
Very rare	Pancreatitis
Hepatobiliary Disorders	
Very rare	Serious hepatotoxicity (including some cases of fatal acute liver failure)
Skin and Subcutaneous Tissue Disorders	
Very rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalized exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity

Investigations	
Very rare	Blood creatine phosphokinase increased

INTERACTIONS

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Similarly, itraconazole may modify the pharmacokinetics of other substances that share this metabolic pathway. Itraconazole is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. When using concomitant medication, it is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust the dosages.

Drugs that may decrease itraconazole plasma concentrations

Drugs that reduce the gastric acidity (e.g. acid neutralizing medicines such as aluminum hydroxide, or acid secretion suppressors such as H2-receptor antagonists and proton pump inhibitors) impair the absorption of itraconazole from itraconazole capsules. It is recommended that these drugs be used with caution when coadministered with itraconazole capsules:

It is recommended that itraconazole be administered with an acidic beverage (such as non-diet cola) upon co-treatment with drugs reducing gastric acidity.

It is recommended that acid neutralizing medicines (e.g. aluminum hydroxide) be administered at least 1 hour before or 2 hours after the intake of TRADENAME capsules.

Upon coadministration, it is recommened that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Coadministration of itraconaozle with potent enzyme inducers of CYP3A4 may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be reduced. Examples include:

Antibacterials: isoniazid, rifabutin (see also under Drugs that may have their plasma concentrations increased by itraconazole), rifampicin.

Anticonvulsants: carbamazepine, (see also under Drugs that may have their plasma concentrations increased by itraconazole), phenobarbital, phenytoin.

Antivirals: efavirenz, nevirapine.

Therefore, administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these drugs be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Drugs that may increase itraconazole plasma concentrations

Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole. Examples include:

Antibacterials: ciprofloxacin, clarithromycin, erythromycin,

Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir (see also under Drugs that may have their plasma concentrations increased by itraconazole), ritonavir (see also under Drugs that may have their plasma concentrations increased by itraconazole),

It is recommended that these drugs be used with caution when coadministered with itraconazole capsules. It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured.

Drugs that may increase intraconazole plasma concentrations

Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole. Examples include:
Antibacterials: ciprofloxacin, clarithromycin, erythromycin,
Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir (see also under **Drugs that may have their plasma concentrations increased by itraconazole**), ritonavir (see also under **Drugs that may have their plasma concentrations increased by itraconazole**),
It is recommended that these drugs be used with caution when coadministered with itraconazole capsules. It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured.

Drugs that may have their plasma concentrations increased by itraconazole

Itraconazole and its major metabolite, hydroxyl-itraconazole, can inhibit the metabolism of medicines metabolised by CYP3A4 and can inhibit the drug transport by P-glycoprotein, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs.CYP3A4-metabolized drugs known to prolong the QT interval may be contraindicated with itraconazole, since the combination may lead to ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. . Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors, the decline in plasma concentrations may be even more gradual. This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.
The interacting drugs are categorized as follows:

- 'Contraindicated': Under no circumstances is the drug to be coadministered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.
- 'Not recommended': It is recommended that the use of the drug be avoided during and up to two weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured.
- 'Use with caution': Careful monitoring is recommended when the drug is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured.

Examples of drugs that may have their plasma concentrations increased by itraconazole presented by drug class with advice regarding coadministration with itraconazole:

Drug Class	Contraindicated	Not Recommended	Use with Caution
Alpha blockers		tamsulosin	

Analgesics	levacetylmethadol (levomethadyl), methadone	fentanyl	alfentanil, buprenorphine IV and sublingual, oxycodone sufentanil
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin
Antibacterials		apixaban, rifabutin[a]	
Anticoagulants and Antiplatelet Drugs		rivaroxaban	coumarins, cilostazol, dabigatran
Anticonvulsants		carbamazepine[a]	
Antidiabetics			repaglinide, saxagliptin
Antihelmintics and Antiprotozoals	halofantrine		praziquantel
Antihistamines	astemizole, mizolastine, terfenadine		Bilastine, ebastine
Antimigraine drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), methylergometrine (methylergonovine)		eletriptan
Antineoplastics	irinotecan	dasatinib, nilotinib, sunitinib, trabectedin	bortezomib, busulphan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, oral midazolam, pimozide, sertindole, triazolam		alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone
Antivirals		simeprevir	maraviroc, indinavir[b], ritonavir[b], saquinavir
Beta Blockers			nadolol
Calcium Channel Blockers	bepridil, felodipine, lercanidipine, nisoldipine		other dihydropyridines, verapamil
Cardiovascular Drugs, Miscellaneous	ivabradine, ranolazine	aliskiren	riociguat
Diuretics	eplerenone		

Gastrointestinal Drugs	Cisapride		aprepitant, domperidone
Immunosuppressants		everolimus	budesonide, ciclesonide, cyclosporine, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus
Lipid Regulating Drugs	lovastatin, simvastatin		atorvastatin
Respiratory Drugs		salmeterol	
SSRIs, Tricyclics and Related Antidepressants			reboxetine
Urological Drugs		vardenafil	fesoterodine. imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine
Other	colchicine, in subjects with renal or hepatic impairment	colchicine	alitretinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan

[a] See also under Drugs that may decrease itraconazole plasma concentrations
[b] See also under Drugs that may increase itraconazole plasma concentrations

Drugs that may have their plasma concentrations decreased by itraconazole
Coadministration of itraconazole with the NSAID meloxicam may decrease the plasma concentrations of meloxicam. It is recommended that meloxicam be used with caution when coadministered with itraconazole, its effects or side effects be monitored. It is recommended that the dosage of meloxicam, if coadministered with itraconazole, be adapted if necessary.

Paediatric Population
Interaction studies have only been performed in adults.

OVERDOSAGE

Symptoms and Signs

In general, adverse events reported with overdose have been consistent with those reported for itraconazole use.

Treatment

In the event of accidental overdosage, supportive measures should be employed. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

PHARMACEUTICAL PRECAUTIONS

Shelf Life

2 years when stored below 25°C. Discard 3 months after opening the bottle.

MEDICINE CLASSIFICATION

Prescription Medicine

PACKAGE QUANTITIES

150 mL

FURTHER INFORMATION

SPORANOX oral solution contains hydroxypropyl-beta-cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour 1, cherry flavour 2, caramel flavour, saccharin sodium, sodium hydroxide and purified water.

Itraconazole

Carcinogenesis, mutagenicity, impairment of fertility

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels of up to 80 mg/kg/day. Male rats treated with 25 mg/kg/day had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolaemia, which is a response of rats, but not dogs or humans to chronic itraconazole administration. Female rats treated with 50 mg/kg/day had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Itraconazole produced no mutagenic effects when assayed in appropriate bacterial, non-mammalian and mammalian test systems.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day even though parental toxicity was present at this dosage level.

Toxicology

In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day. The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones and increased bone fragility. At a dosage level of 80 mg/kg/day over one year or 160 mg/kg/day for six months, itraconazole induced small tooth pulp with hypocellular appearance in some rats.

Increased relative adrenal weights and swollen adrenals (reversible) were seen in rats and dogs where plasma levels were comparable to those of human therapeutic doses. Adrenocortical function was not affected in studies in humans after the recommended daily doses; with higher doses (600 mg/day for 3 months), adrenal cortex response to ACTH stimulation was reduced in 1 of 8 patients, but returned to normal when the dosage was reduced.

Microbiology

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.

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 >1 μg/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, C. tropicalis, C. parapsilosis* and *C. krusei, Cryptococcus neoformans, Malassezia* spp*., Trichosporon* spp*., Geotrichum* spp*.); Aspergillus* spp*.; Histoplasma* spp*.,* including *H. capsulatum; Paracoccidioides brasiliensis; Sporothrix schenckii; Fonsecaea* spp*.; Cladosporium* spp*.; Blastomyces dermatitidis; Coccidiodes 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.

Hydroxypropyl-beta-Cyclodextrin

Single and repeated dose toxicity studies in mice, rats and dogs indicate a wide safety margin after oral and intravenous administration of hydroxypropyl-beta-cyclodextrin. Most effects were adaptive in nature (histological changes in the urinary tract, softening of feces related to the osmotic water retention in the large intestine, activation of the mononuclear phagocyte system) and showed good reversibility.
Slight liver changes occurred at doses of about 30 times the proposed human dose of hydroxypropyl-beta-cyclodextrin.
Oral treatment of juvenile Beagle dogs with hydroxypropyl-beta-cyclodextrin at 1200 mg/kg for a period of up to 13 weeks with a 4-week recovery period was clinically well tolerated with no effects noted when compared to control animals at laboratory or histopathology examination.

Carcinogenicity and Mutagenicity

No primary carcinogenicity activity was evidenced in the mouse carcinogenicity study. In the rat carcinogenicity study, an increased incidence of neoplasms in the large intestine (at 5000 mg/kg/day) and in the exocrine pancreas (from 500 mg/kg/day) were seen. Based on a human equivalent dose calculation normalized for body surface area, the recommended clinical dose of SPORANOX oral solution contains approximately 1.7 times the amount of hydroxypropyl-beta-cyclodextrin as was in the 500 mg/kg/day dose administered in rats in this carcinogenicity study.
The slightly higher incidence of adenocarcinomas in the large intestines was linked to the hypertrophic/hyperplastic and inflammatory changes in the colonic mucosa brought about by hydroxypropyl-beta-cyclodextrin -induced increased osmotic forces and is considered to be of low clinical relevance. Development of the pancreatic tumors is related to the mitogenic

action of cholecystokinin in rats. This finding was not observed in the mouse carcinogenicity study, nor in a 12-month toxicity study in dogs or in a 2-year toxicity study in female cynomolgus monkeys. There is no evidence that cholecystokinin has a mitogenic action in man. However, the clinical relevance of these findings is not applicable.
hydroxypropyl-beta-cyclodextrin has no antifertile, no direct embryotoxic and no teratogenic effect, and is not mutagenic. The chemical structure of hydroxypropyl-beta-cyclodextrin does not raise suspicion for genotoxic activity. Tests on DNA-damage, gene mutations and chromosome aberrations in vitro and in vivo did not reveal any genotoxic activity.

Reproductive Toxicology
hydroxypropyl-beta-cyclodextrin has no direct embryotoxic and no teratogenic effect,

Fertility
Hydroxypropyl-beta-cyclodextrin had no effect on fertility when administered to male and female rats at dietary doses up to 5 g/kg/day or IV doses up to 400 mg/kg/day.

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