SPORANOX®
(itraconazole)
Oral Solution

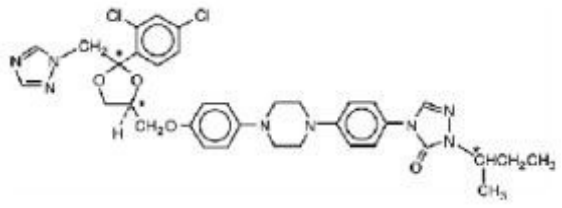
BOXED WARNING

Congestive Heart Failure, Cardiac Effects and Drug Interactions: If signs or symptoms of congestive heart failure occur during administration of SPORANOX® (itraconazole) Oral Solution, continued SPORANOX® use should be reassessed. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations for more information.)

Drug Interactions: Coadministration of the following drugs are contraindicated with SPORANOX® Oral Solution: methadone, disopyramide, dofetilide, dronedarone, quinidine, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, lovastatin, simvastatin, ticagrelor, and, in subjects with varying degrees of renal or hepatic impairment, colchicine, fesoterodine, telithromycin and solifenacin. See PRECAUTIONS: Drug Interactions Section for specific examples. Coadministration with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia. See CONTRAINDICATIONS and WARNINGS Sections, and PRECAUTIONS: Drug Interactions Section for specific examples.

DESCRIPTION

SPORANOX® is the brand name for itraconazole, an azole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:



(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one

or

(±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

SPORANOX® (itraconazole) Oral Solution contains 10 mg of itraconazole per mL, solubilized by hydroxypropyl-β-cyclodextrin (400 mg/mL) as a molecular inclusion complex. SPORANOX® Oral Solution is clear and yellowish in color with a target pH of 2. Other ingredients are hydrochloric acid, propylene glycol, purified water, sodium hydroxide, sodium saccharin, sorbitol, cherry flavor 1, cherry flavor 2 and caramel flavor.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism:

Itraconazole

General Pharmacokinetic Characteristics

Peak plasma concentrations are reached within 2.5 hours following administration of the oral solution. 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} and AUC values 4 to 7-fold higher than those seen after a single dose. Steady-state C_{max} values of about 2 μg/ml are reached after oral administration of 200 mg once daily. 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 administration of the oral solution. Peak plasma concentrations of itraconazole are reached within 2.5 hours following administration of the oral solution under fasting conditions. 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. Itraconazole exposure is greater with the oral solution than with the capsule formulation when the same dose of drug is given. (see WARNINGS)

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.

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.

Special Populations:

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 oral dose of itraconazole 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 PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

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 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 CONTRAINDICATIONS, PRECAUTIONS: Drug Interactions and DOSAGE AND ADMINISTRATION.)

Decreased Cardiac Contractility:

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole intravenous infusion, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of SPORANOX® Oral Solution, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX® Oral Solution administration. (See BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Cystic Fibrosis:

Seventeen cystic fibrosis patients, ages 7 to 28 years old, were administered itraconazole oral solution 2.5 mg/kg b.i.d. for 14 days in a pharmacokinetic study. Sixteen patients completed the study. Steady state trough concentrations >250 ng/mL were achieved in 6 out of 11 patients ≥16 years of age but in none of the 5 patients <16 years of age. Large variability was observed in the pharmacokinetic data (%CV for trough concentrations = 98% and 70% for ≥16 and <16 years, respectively; %CV for AUC = 75% and 58% for ≥16 and <16 years, respectively). If a patient with cystic fibrosis does not respond to SPORANOX® Oral Solution, consideration should be given to switching to alternative therapy.

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.

MICROBIOLOGY

Mechanism of Action:

In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Drug Resistance:

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

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

Itraconazole is not active against *Zygomycetes* (e.g., *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

Cross-resistance:

In systemic candidosis, if fluconazole-resistant strains of *Candida* species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of itraconazole therapy.

Several *in vitro* studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors,

including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed.

Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ^{14}C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

Activity In Vitro and in Clinical Infections:

Itraconazole has been shown to be active against most strains of the following microorganism, **both *in vitro* and in clinical infections.**

Candida albicans

Susceptibility Testing Methods

(Applicable to Candida isolates from patients with oropharyngeal or esophageal candidiasis)

Candida albicans

The interpretive criteria and breakpoints for itraconazole against *Candida albicans* are applicable to tests performed using Clinical Laboratory and Standards Institute (CLSI) microbroth dilution reference method M27A for MIC (partial inhibition endpoint) read at 48 hours.

Broth Microdilution Techniques

Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *Candida* spp. to antifungal agents. MICs should be determined using a standardized procedure at 48 hours. Standardized procedures are based on a microdilution method (broth)[1,2] with standardized inoculum concentrations and standardized concentrations of itraconazole powder. The MIC values should be interpreted according to the criteria provided in Table below:

Susceptibility Interpretive Criteria for Itraconazole[1,2]			
Pathogen	**Broth Microdilution MIC* (µg/mL) at 48 Hours**		
	S	I	R
Candida albicans	≤ 0.125	0.25 – 0.5	≥ 1

* A report of *Susceptible (S)* indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate* (I) category indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in the body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. The *intermediate* category is sometimes called *Susceptible-Dose Dependent* (SDD) and both categories are equivalent for itraconazole. A report of *Resistant* (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard itraconazole powder should provide the following range of values noted in the table below.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

Acceptable Quality Control Ranges for Itraconazole to be used in Validation of Susceptibility Test Results[1,2]	
QC Strain	**Broth Microdilution MIC (µg/mL) at 48 Hours**
Candida parapsilosis ATCC† 22019	0.06-0.25
Candida krusei ATCC 6258	0.12-0.5

† ATCC is the registered trademark of the American Type Culture Collection.

CLINICAL STUDIES

Oropharyngeal Candidiasis:

Two randomized, controlled studies for the treatment of oropharyngeal candidiasis have been conducted (total n=344). In one trial, clinical response to either 7 or 14 days of itraconazole oral solution, 200 mg/day, was similar to fluconazole tablets and averaged 84% across all arms. Clinical response in this study was defined as cured or improved (only minimal signs and symptoms with no visible lesions). Approximately 5% of subjects were lost to follow-up before any evaluations could be performed. Response to 14 days therapy of itraconazole oral solution was associated with a lower relapse rate than 7 days of itraconazole therapy. In another trial, the clinical response rate (defined as cured or improved) for itraconazole oral solution was

similar to clotrimazole troches and averaged approximately 71% across both arms, with approximately 3% of subjects lost to follow-up before any evaluations could be performed. Ninety-two percent of the patients in these studies were HIV seropositive.

In an uncontrolled, open-label study of selected patients clinically unresponsive to fluconazole tablets (n=74, all patients HIV seropositive), patients were treated with itraconazole oral solution 100 mg b.i.d. (Clinically unresponsive to fluconazole in this study was defined as having received a dose of fluconazole tablets at least 200 mg/day for a minimum of 14 days.) Treatment duration was 14-28 days based on response. Approximately 55% of patients had complete resolution of oral lesions. Of patients who responded and then entered a follow-up phase (n=22), all relapsed within 1 month (median 14 days) when treatment was discontinued. Although baseline endoscopies had not been performed, several patients in this study developed symptoms of esophageal candidiasis while receiving therapy with itraconazole oral solution. Itraconazole oral solution has not been directly compared to other agents in a controlled trial of similar patients.

Esophageal Candidiasis:

A double-blind randomized study (n=119, 111 of whom were HIV seropositive) compared itraconazole oral solution (100 mg/day) to fluconazole tablets (100 mg/day). The dose of each was increased to 200 mg/day for patients not responding initially. Treatment continued for 2 weeks following resolution of symptoms, for a total duration of treatment of 3-8 weeks. Clinical response (a global assessment of cured or improved) was not significantly different between the two study arms, and averaged approximately 86% with 8% lost to follow-up. Six of 53 (11%) itraconazole-treated patients and 12/57 (21%) fluconazole-treated patients were escalated to the 200 mg dose in this trial. Of the subgroup of patients who responded and entered a follow-up phase (n=88), approximately 23% relapsed across both arms within 4 weeks.

INDICATIONS AND USAGE

SPORANOX® (itraconazole) Oral Solution is indicated for the treatment of oropharyngeal and esophageal candidiasis.

(See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

CONTRAINDICATIONS

Congestive Heart Failure:

SPORANOX® (itraconazole) 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 BOXED WARNING, WARNINGS, PRECAUTIONS: Drug Interactions-Calcium Channel Blockers, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations.)

Drug Interactions:

Coadministration of a number of CYP3A4 substrates are contraindicated with SPORANOX®. Plasma concentrations increase for the following drugs: methadone, disopyramide, dofetilide, dronedarone, quinidine, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, lovastatin, simvastatin, ticagrelor and, in subjects with varying degrees of renal or hepatic impairment, colchicine, fesoterodine, telithromycin and solifenacin. (See PRECAUTIONS: Drug Interactions Section for specific examples.) This increase in drug concentrations caused by coadministration with itraconazole may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Specific examples are listed in PRECAUTIONS: Drug Interactions.

SPORANOX® is contraindicated for patients who have shown hypersensitivity to itraconazole. There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing SPORANOX® to patients with hypersensitivity to other azoles.

WARNINGS

Hepatic Effects:

SPORANOX® has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition, and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Continued SPORANOX® use or reinstitution of treatment with SPORANOX® is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS.**)

Cardiac Dysrhythmias:

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as cisapride, pimozide, methadone, or quinidine concomitantly with SPORANOX® and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with SPORANOX® is contraindicated. (See BOXED WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

Cardiac Disease:

SPORANOX® Oral Solution should not be used in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk. For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of SPORANOX® therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of SPORANOX® Oral Solution, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX® Oral Solution administration.

Itraconazole has been shown to have a negative inotropic effect. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole intravenous infusion, transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

SPORANOX® has been associated with reports of congestive heart failure. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg although there were also cases reported among those receiving lower total daily doses.

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. Concomitant administration of SPORANOX® and felodipine or nisoldipine is contraindicated.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CONTRAINDICATIONS, CLINICAL PHARMACOLOGY: Special

Populations, PRECAUTIONS: Drug Interactions, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Interaction potential:

SPORANOX® has a potential for clinically important drug interactions. 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 PRECAUTIONS: Drug Interactions.

Interchangeability:

SPORANOX® (itraconazole) Oral Solution and SPORANOX® Capsules should not be used interchangeably. This is because drug exposure is greater with the Oral Solution than with the Capsules when the same dose of drug is given. Only SPORANOX® Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis.

Hydroxypropyl-β-cyclodextrin:

SPORANOX® Oral Solution contains the excipient hydroxypropyl-β-cyclodextrin which produced adenocarcinomas in the large intestine and exocrine pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these adenocarcinomas is unknown. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Treatment of Severely Neutropenic Patients:

SPORANOX® Oral Solution as treatment for oropharyngeal and/or esophageal candidiasis was not investigated in severely neutropenic patients. Due to its pharmacokinetic properties, SPORANOX® Oral Solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis.

PRECAUTIONS

Hepatotoxicity:

Rare cases of serious hepatotoxicity have been observed with SPORANOX® treatment, including some cases within the first week. It is recommended that liver function monitoring be considered in all patients receiving SPORANOX®. Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction.

Neuropathy:

If neuropathy occurs that may be attributable to SPORANOX® Oral Solution, the treatment should be discontinued.

Cystic Fibrosis:

If a patient with cystic fibrosis does not respond to SPORANOX® Oral Solution, consideration should be given to switching to alternative therapy (see CLINICAL PHARMACOLOGY: Special Populations).

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 BOXED WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Information for Patients:

- Only SPORANOX® Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis.
- SPORANOX® Oral Solution contains the excipient hydroxypropyl-β-cyclodextrin which produced adenocarcinomas in the large intestine and exocrine pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these adenocarcinomas is unknown. (See Carcinogenesis, Mutagenesis, and Impairment of Fertility.)
- Taking SPORANOX® Oral Solution under fasted conditions improves the systemic availability of itraconazole. Instruct patients to take SPORANOX® Oral Solution without food, if possible.
- SPORANOX® Oral Solution should not be used interchangeably with SPORANOX® Capsules.
- Instruct patients about the signs and symptoms of congestive heart failure, and if these signs or symptoms occur during SPORANOX® administration, they should discontinue SPORANOX® and contact their healthcare provider immediately.
- Instruct patients to stop SPORANOX® treatment immediately and contact their healthcare provider if any signs and symptoms suggestive of liver dysfunction develop. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine, or pale stools.
- Instruct patients to contact their physician before taking any concomitant medications with itraconazole to ensure there are no potential drug interactions.
- Instruct patients that hearing loss can occur with the use of itraconazole. The hearing loss usually resolves when treatment is stopped, but can persist in some patients. Advise patients to discontinue therapy and inform their physicians if any hearing loss symptoms occur.

- Instruct patients that dizziness or blurred/double vision can sometimes occur with itraconazole. Advise patients that if they experience these events, they should not drive or use machines.

Drug Interactions:

Itraconazole is mainly metabolized through CYP3A4. Other drugs that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Similarly, itraconazole may modify the pharmacokinetics of other drugs 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 dosages.

Drugs that may decrease itraconazole plasma concentrations

Coadministration of itraconazole 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') and telaprevir.

It is recommended that these drugs be used with caution when coadministered with itraconazole oral solution. 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.

Drugs that may have their plasma concentrations increased by itraconazole

Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of drugs metabolized 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 torsade 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.

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

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
	Under no circumstances is the drug to be coadministered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.	*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. The label of the coadministered drug should be consulted for information on dose adjustment and adverse effects.*	*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. The label of the coadministered drug should be consulted for information on dose adjustment and adverse effects.*	
Alpha Blockers		tamsulosin		

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
Analgesics	methadone		alfentanil, buprenorphine IV and sublingual, fentanyl, oxycodone, sufentanil	**Methadone:** The potential increase in plasma concentrations of methadone when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation and *torsade de pointes*. **Fentanyl:** The potential increase in plasma concentrations of fentanyl when coadministered with SPORANOX® may increase the risk of potentially fatal respiratory depression. **Sufentanil:** No human pharmacokinetic data of an interaction with itraconazole are available. In vitro data suggest that sufentanil is metabolized by CYP3A4 and so potentially increased sufentanil plasma concentrations would be expected when coadministered with SPORANOX®.
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin	**Disopyramide, dofetilide, dronedarone, quinidine:** The potential increase in plasma concentrations of these drugs when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
Antibacterials	telithromycin, in subjects with severe renal impairment or severe hepatic impairment	rifabutin	telithromycin	**Telithromycin:** The potential increase in plasma concentrations of telithromycin in subjects with severe renal impairment or severe hepatic impairment, when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QT prolongation and torsade de pointes. **Rifabutin:** See also under 'Drugs that may decrease itraconazole plasma concentrations'.
Anticoagulants and Antiplatelet Drugs	ticagrelor	apixaban, rivaroxaban	coumarins, cilostazol, dabigatran	**Ticagrelor:** The potential increase in plasma concentrations of ticagrelor may increase the risk of bleeding. **Coumarins:** SPORANOX® may enhance the anticoagulant effect of coumarin-like drugs, such as warfarin.

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
Anticonvulsants		carbamazepine		**Carbamazepine:** *In vivo* studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX® and carbamazepine may inhibit the metabolism of carbamazepine. See also under 'Drugs that may decrease itraconazole plasma concentrations'.
Antidiabetics			repaglinide, saxagliptin	
Antihelmintics and Antiprotozoals			praziquantel	
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)		eletriptan	**Ergot Alkaloids:** The potential increase in plasma concentrations of ergot alkaloids when coadministered with SPORANOX® may increase the risk of ergotism, ie. a risk for vasospasm potentially leading to cerebral ischemia and/or ischemia of the extremities.

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
Antineoplastics	irinotecan	axitinib, dabrafenib, dasatinib, ibrutinib, nilotinib, sunitinib, trabectedin	bortezomib, busulphan, docetaxel, erlotinib, gefitinib, imatinib, ixabepilone, ponatinib, lapatinib, trimetrexate, vinca alkaloids	**Irinotecan:** The potential increase in plasma concentrations of irinotecan when coadministered with SPORANOX® may increase the risk of potentially fatal adverse events.
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, oral midazolam, pimozide, triazolam		alprazolam, aripiprazole, buspirone, diazepam, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone	**Midazolam, triazolam**: Coadministration of SPORANOX® and oral midazolam, or triazolam may cause several-fold increases in plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. **Pimozide:** The potential increase in plasma concentrations of pimozide when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation and *torsade de pointes*.
Antivirals		simprevir	maraviroc, indinavir, ritonavir, saquinavir	**Indinavir, ritonavir:** See also under 'Drugs that may increase itraconazole plasma concentrations'.
Beta Blockers			nadolol	

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
Calcium Channel Blockers	felodipine, nisoldipine		other dihydropyridines, verapamil	**Calcium channel blockers** can have a negative inotropic effect which may be additive to those of itraconazole. The potential increase in plasma concentrations of calcium channel blockers when co-administered with SPORANOX® may increase the risk of congestive heart failure. **Dihydropyridines:** Concomitant administration of SPORANOX® may cause several-fold increases in plasma concentrations of dihydropyridines. Edema has been reported in patients concomitantly receiving SPORANOX® and dihydropyridine calcium channel blockers.
Cardiovascular Drugs, Miscellaneous	ivabradine, ranolazine	aliskiren, sildenafil, for the treatment of pulmonary hypertension	bosentan, riociguat	**Ivabradine:** The potential increase in plasma concentrations of ivabradine when coadministered with SPORANOX® may increase the risk of ivabradine-related adverse events, such as atrial fibrillation, bradycardia, sinus arrest and heart block. **Ranolazine:** The potential increase in plasma concentrations of ranolazine when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.
Diuretics	eplerenone			**Eplerenone:** The potential increase in plasma concentrations of eplerenone when coadministered with SPORANOX® may increase the risk of hyperkalemia and hypotension.

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
Gastrointestinal Drugs	cisapride		aprepitant	**Cisapride:** The potential increase in plasma concentrations of cisapride when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.
Immunosuppressants		everolimus, temsirolimus	budesonide, ciclesonide, cyclosporine, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus	
Lipid Regulating Drugs	lovastatin, simvastatin		atorvastatin	The potential increase in plasma concentrations of atorvastatin, lovastatin, and simvastatin when coadministered with SPORANOX® may increase the risk of skeletal muscle toxicity, including rhabdomyolysis.
Respiratory Drugs		salmeterol		

Table 1: Drugs that may have their plasma concentrations increased by itraconazole				
Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**	**Comments**
Urological Drugs	fesoterodine, in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment, solifenacin, in subjects with severe renal impairment or moderate to severe hepatic impairment	darifencin, vardenafil	fesoterodine, oxybutynin sildenafil, for the treatment of erectile dysfunction, solifenacin, tadalafil, tolterodine	**Fesoterodine:** The potential increase in plasma concentrations of the fesoteridine active metabolite may be greater in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment, which may lead to an increased risk of adverse reactions. **Solifenacin:** The potential increase in plasma concentrations of solifenacin in subjects with severe renal impairment or moderate to severe hepatic impairment, when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QT prolongation.
Other	colchicine, in subjects with renal or hepatic impairment	colchicine, conivaptan, tolvaptan	cinacalcet	**Colchicine:** The potential increase in plasma concentrations of colchicine when coadministered with SPORANOX® may increase the risk of potentially fatal adverse events. **Conivaptan and Tolvaptan:** A safe and effective dose of either conivaptan or tolvaptan has not been established when coadministered with SPORANOX®.

Drugs that may have their plasma concentrations decreased by itraconazole

Coadministration of itraconazole with the NSAID meloxicam may decrease the plasma concentration of meloxicam. It is recommended that meloxicam be used with caution when coadministered with itraconazole, and its effects or side effects be monitored. It is recommended that the dosage of meloxicam, if coadministered with itraconazole, be adjusted if necessary.

Pediatric Population

Interaction studies have only been performed in adults.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Itraconazole

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10x the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1x MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25x MRHD) 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 DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5x MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20x MRHD).

Hydroxypropyl-β-cyclodextrin (HP-β-CD)

Hydroxypropyl-β-cyclodextrin (HP-β-CD) is the solubilizing excipient used in SPORANOX® Oral Solution.

Hydroxypropyl-β-cyclodextrin (HP-β-CD) was found to produce neoplasms in the large intestine at 5000 mg/kg/day in rat carcinogenicity study. This dose was about 6 times amount contained in the recommended clinical dose of SPORANOX® Oral Solution based on body surface area comparisons. The clinical relevance of this finding is unknown. 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 HP-β-CD-induced increased osmotic forces.

In addition, HP-β-CD was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animals were not seen in the untreated group and are not reported in the historical controls. The recommended clinical dose of SPORANOX® Oral Solution contains approximately 1.7 times the amount of HP-β-CD as was in the 500 mg/kg/day dose, based on body surface area comparisons. This finding was not observed in the mouse carcinogenicity study at doses of 500, 2000 or 5000 mg/kg/day for 22-23 months. This finding was also not observed in a 12-month toxicity study in dogs or in a 2-year toxicity study in female cynomolgus monkeys.

Since the development of the pancreatic tumors may be related to a mitogenic action of cholecystokinin and since there is no evidence that cholecystokinin has a mitogenic action in man, the clinical relevance of these findings is unknown.

HP-β-CD has no antifertile effect, and is not mutagenic.

Pregnancy: Teratogenic effects. Pregnancy Category C:

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20x MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10x MRHD). Itraconazole has been shown to cross the placenta in a rat model. In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

SPORANOX® Oral Solution contains the excipient hydroxypropyl-β-cyclodextrin (HP-β-CD). HP-β-CD has no direct embryotoxic and no teratogenic effect.

There are no studies in pregnant women. SPORANOX® should be used in pregnancy only if the benefit outweighs the potential risk.

During post-marketing experience, cases of congenital abnormalities have been reported. (See ADVERSE REACTIONS: Post-marketing Experience.)

Nursing Mothers:

Itraconazole is excreted in human milk; therefore, the expected benefits of SPORANOX® therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid potential transmission of HIV to uninfected infants.

Pediatric Use:

The efficacy and safety of SPORANOX® have not been established in pediatric patients.

The long-term effects of itraconazole on bone growth in children are unknown. In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5x MRHD). 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 (10x MRHD) over 1 year or 160 mg/kg/day (20x MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats.

Geriatric Use:

Clinical studies of SPORANOX® Oral Solution did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. 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.

Transient or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see BOXED WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions).

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 impairment. Caution should be exercised when itraconazole is administered in this patient population and dose adjustment may be needed. (See CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION.)

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. It is recommended that patients with impaired hepatic function be carefully monitored when taking SPORANOX®. It is recommended that the prolonged elimination half-life of 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 CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

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.

SPORANOX® has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. The risks and benefits of SPORANOX® use should be reassessed. (See WARNINGS: Hepatic Effects and PRECAUTIONS: Hepatotoxicity and Information for Patients.)

Adverse Events Reported in Oropharyngeal or Esophageal Candidiasis Trials

U.S. adverse experience data are derived from 350 immunocompromised patients (332 HIV seropositive/AIDS) treated for oropharyngeal or esophageal candidiasis. Table 2 below lists adverse events reported by at least 2% of patients treated with SPORANOX® Oral Solution in U.S. clinical trials. Data on patients receiving comparator agents in these trials are included for comparison.

Table 2: Summary of Adverse Events Reported by ≥2% of SPORANOX® Treated Patients in U.S. Clinical Trials (Total)

Body System/ Adverse	Itraconazole			
	Total	All	Fluconazole	Clotrimazole (n = 81‡) %

Event	(n = 350[*]) %	controlled studies (n = 272) %	(n = 125[†]) %	
Gastrointestinal disorders				
Nausea	11	10	11	5
Diarrhea	11	10	10	4
Vomiting	7	6	8	1
Abdominal pain	6	4	7	7
Constipation	2	2	1	0
Body as a whole				
Fever	7	6	8	5
Chest pain	3	3	2	0
Pain	2	2	4	0
Fatigue	2	1	2	0
Respiratory disorders				
Coughing	4	4	10	0
Dyspnea	2	3	5	1
Pneumonia	2	2	0	0
Sinusitis	2	2	4	0
Sputum increased	2	3	3	1
Skin and appendages disorders				
Rash	4	5	4	6
Increased sweating	3	4	6	1
Skin disorder unspecified	2	2	2	1
Central/peripheral nervous system				
Headache	4	4	6	6
Dizziness	2	2	4	1
Resistance mechanism disorders				
Pneumocystis carinii infection	2	2	2	0
Psychiatric disorders				
Depression	2	1	0	1

[*] Of the 350 patients, 209 were treated for oropharyngeal candidiasis in controlled studies, 63 were treated for esophageal candidiasis in controlled studies and 78 were treated for oropharyngeal candidiasis in an open study.

[†] Of the 125 patients, 62 were treated for oropharyngeal candidiasis and 63 were treated for esophageal candidiasis.

[‡] All 81 patients were treated for oropharyngeal candidiasis.

Adverse events reported by less than 2% of patients in U.S. clinical trials with SPORANOX® included: adrenal insufficiency, asthenia, back pain, dehydration, dyspepsia, dysphagia, flatulence, gynecomastia, hematuria, hemorrhoids, hot flushes, implantation complication, infection unspecified, injury, insomnia, male breast pain, myalgia, pharyngitis, pruritus, rhinitis, rigors, stomatitis ulcerative, taste perversion, tinnitus, upper respiratory tract infection, vision abnormal, and weight decrease. Edema, hypokalemia and menstrual disorders have been reported in clinical trials with itraconazole capsules.

Adverse Events Reported from Other Clinical Trials

A comparative clinical trial in patients who received intravenous itraconazole followed by SPORANOX® Oral Solution or received Amphotericin B reported the following adverse events in the itraconazole intravenous/SPORANOX® Oral Solution treatment arm which are not listed above in the subsection "Adverse Events Reported in Oropharnyngeal or Esophageal Candidiasis Trials" or listed below as postmarketing reports of adverse drug reactions: serum creatinine increased, blood urea nitrogen increased, renal function abnormal, hypocalcemia, hypomagnesemia, hypophosphatemia, hypotension, tachycardia and pulmonary infiltration.

In addition, the following adverse drug reactions were reported in patients who participated in SPORANOX® Oral Solution clinical trials:

Cardiac Disorders: cardiac failure;

General Disorders and Administration Site Conditions: edema;

Hepatobiliary Disorders: hepatic failure, hyperbilirubinemia;

Metabolism and Nutrition Disorders: hypokalemia;

Reproductive System and Breast Disorders: menstrual disorder

The following is a list of additional adverse drug reactions associated with itraconazole that have been reported in clinical trials of SPORANOX® Capsules and itraconazole IV excluding the adverse reaction term "Injection site inflammation" which is specific to the injection route of administration:

Cardiac Disorders: left ventricular failure;

Gastrointestinal Disorders: gastrointestinal disorder;

General Disorders and Administration Site Conditions: face edema;

Hepatobiliary Disorders: jaundice, hepatic function abnormal;

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, gamma-glutamyltransferase increased, urine analysis abnormal;

Metabolism and Nutrition Disorders: hyperglycemia, hyperkalemia;

Nervous System Disorders: somnolence;

Psychiatric Disorders: confusional state;

Renal and Urinary Disorders: renal impairment;

Respiratory, Thoracic and Mediastinal Disorders: dysphonia;

Skin and Subcutaneous Tissue Disorders: rash erythematous;

Vascular Disorders: hypertension

In addition, the following adverse drug reaction was reported in children only who participated in SPORANOX® Oral Solution clinical trials: mucosal inflammation.

Post-marketing Experience

Adverse drug reactions that have been first identified during post-marketing experience with SPORANOX® (all formulations) are listed in the table below. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 3: Postmarketing Reports of Adverse Drug Reactions

Blood and Lymphatic System Disorders:	Leukopenia, neutropenia, thrombocytopenia
Immune System Disorders:	Anaphylaxis; anaphylactic, anaphylactoid and allergic reactions; serum sickness; angioneurotic edema
Metabolism and Nutrition Disorders:	Hypertriglyceridemia
Nervous System Disorders:	Peripheral neuropathy, paresthesia, hypoesthesia, tremor
Eye Disorders:	Visual disturbances, including vision blurred and diplopia
Ear and Labyrinth Disorders:	Transient or permanent hearing loss
Cardiac Disorders:	Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders:	Pulmonary edema
Gastrointestinal Disorders:	Pancreatitis
Hepatobiliary Disorders:	Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes

Skin and Subcutaneous Tissue Disorders:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, alopecia, photosensitivity, urticaria
Musculoskeletal and Connective Tissue Disorders:	Arthralgia
Renal and Urinary Disorders:	Urinary incontinence, pollakiuria
Reproductive System and Breast Disorders:	Erectile dysfunction
General Disorders and Administration Site Conditions:	Peripheral edema
Investigations:	Blood creatine phosphokinase increased

There is limited information on the use of SPORANOX® during pregnancy. Cases of congenital abnormalities including skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations have been reported during post-marketing experience. A causal relationship with SPORANOX® has not been established. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

OVERDOSAGE

Itraconazole is not removed by dialysis. In the event of accidental overdosage, supportive measures should be employed. Activated charcoal may be given if considered appropriate.

In general, adverse events reported with overdose have been consistent with adverse drug reactions already listed in this package insert for itraconazole. (See ADVERSE REACTIONS.)

DOSAGE AND ADMINISTRATION

Treatment of Oropharyngeal and Esophageal Candidiasis:

The solution should be vigorously swished in the mouth (10 mL at a time) for several seconds and swallowed.

The recommended dosage of SPORANOX® (itraconazole) Oral Solution for oropharyngeal candidiasis is 200 mg (20 mL) daily for 1 to 2 weeks. Clinical signs and symptoms of oropharyngeal candidiasis generally resolve within several days.

For patients with oropharyngeal candidiasis unresponsive/refractory to treatment with fluconazole tablets, the recommended dose is 100 mg (10 mL) b.i.d. For patients responding to therapy, clinical response will be seen in 2 to 4 weeks. Patients may be expected to relapse shortly after discontinuing therapy. Limited data on the safety of long-term use (>6 months) of SPORANOX® Oral Solution are available at this time.

The recommended dosage of SPORANOX® Oral Solution for esophageal candidiasis is 100 mg (10 mL) daily for a minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg (20 mL) per day may be used based on medical judgment of the patient's response to therapy.

SPORANOX® Oral Solution and SPORANOX® Capsules should not be used interchangeably. Patients should be instructed to take SPORANOX® Oral Solution without food, if possible. Only SPORANOX® Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis.

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. (See CLINICAL PHARMACOLOGY: Special Populations and PRECAUTIONS.)

Use in Patients with 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 CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and PRECAUTIONS.)

HOW SUPPLIED

SPORANOX® (itraconazole) Oral Solution is available in 150 mL amber glass bottles (NDC 50458-295-15) containing 10 mg of itraconazole per mL.

Store at or below 25°C (77°F). Do not freeze.

Keep out of reach of children.

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Product of Belgium

Manufactured by:

Janssen Pharmaceutica NV

Beerse, Belgium

Manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

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2. Clinical and Laboratory Standards Institute (CLSI). *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Fourth Informational Supplement.* CLSI document M27-S4. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2012.