

SPORANOX- itraconazole solution
Janssen Pharmaceuticals, Inc.

SPORANOX®
(itraconazole)
Oral Solution

BOXED WARNINGS

Congestive Heart Failure, Cardiac Effects and Drug Interactions

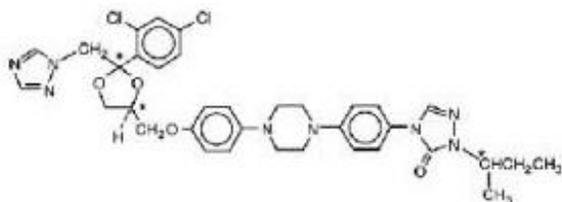
When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur during administration of SPORANOX® (itraconazole) Oral Solution, continued SPORANOX® use should be reassessed. (See CONTRAINDICATIONS,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

Drug Interactions

Coadministration of cisapride, oral midazolam, nisoldipine, felodipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), lovastatin, simvastatin, ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) or methadone with SPORANOX® (itraconazole) Capsules or Oral Solution is contraindicated. SPORANOX®, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, methadone, levacetylmethadol (levomethadyl), or quinidine concomitantly with SPORANOX® and/or other CYP3A4 inhibitors. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

DESCRIPTION

SPORANOX® is the brand name for itraconazole, a synthetic triazole 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]-Δ²-1,2,4-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]-Δ²-1,2,4-triazolin-5-one

or

(±)-1-[(*RS*)-*sec*-butyl]-4-[*p*-[4-[*p*-[[*(2R,4S)*]-2-(2,4-dichlorophenyl)-2-(1*H*-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

NOTE: The plasma concentrations reported below were measured by high-performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported may be higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See MICROBIOLOGY.)

The absolute bioavailability of itraconazole administered as a non-marketed solution formulation under fed conditions was 55% in 6 healthy male volunteers. However, the bioavailability of SPORANOX[®] (itraconazole) Oral Solution is increased under fasted conditions reaching higher maximum plasma concentrations (C_{max}) in a shorter period of time. In 27 healthy male volunteers, the steady-state area under the plasma concentration versus time curve (AUC_{0-24h}) of itraconazole (SPORANOX[®] Oral Solution, 200 mg daily for 15 days) under fasted conditions was $131 \pm 30\%$ of that obtained under fed conditions. Therefore, unlike SPORANOX[®] Capsules, it is recommended that SPORANOX[®] Oral Solution be administered without food. Presented in the table below are the steady-state (Day 15) pharmacokinetic parameters for itraconazole and hydroxyitraconazole (SPORANOX[®] Oral Solution) under fasted and fed conditions:

	Itraconazole		Hydroxyitraconazole	
	Fasted	Fed	Fasted	Fed
C_{max} (ng/mL)	$1963 \pm 601^*$	1435 ± 477	2055 ± 487	1781 ± 397
T_{max} (hours)	2.5 ± 0.8	4.4 ± 0.7	5.3 ± 4.3	4.3 ± 1.2
AUC_{0-24h} (ng·h/mL)	29271 ± 10285	22815 ± 7098	45184 ± 10981	38823 ± 8907
$t_{1/2}$ (hours)	39.7 ± 13	37.4 ± 13	27.3 ± 13	26.1 ± 10

* mean \pm standard deviation

The bioavailability of SPORANOX[®] Oral Solution relative to SPORANOX[®] Capsules was studied in 30 healthy male volunteers who received 200 mg of itraconazole as the oral solution and capsules under fed conditions. The $AUC_{0-\infty}$ from SPORANOX[®] Oral Solution was $149 \pm 68\%$ of that obtained from SPORANOX[®] Capsules; a similar increase was observed for hydroxyitraconazole. In addition, a cross study comparison of itraconazole and hydroxyitraconazole pharmacokinetics following the administration of single 200 mg doses of SPORANOX[®] Oral Solution (under fasted conditions) or SPORANOX[®] Capsules (under fed conditions) indicates that when these two formulations are administered under conditions which optimize their systemic absorption, the bioavailability of the solution relative to capsules is expected to be increased further. Therefore, it is recommended that

SPORANOX[®] Oral Solution and SPORANOX[®] Capsules not be used interchangeably. The following table contains pharmacokinetic parameters for itraconazole and hydroxyitraconazole following single 200 mg doses of SPORANOX[®] Oral Solution (n=27) or SPORANOX[®] Capsules (n=30) administered to healthy male volunteers under fasted and fed conditions, respectively:

	Itraconazole		Hydroxyitraconazole	
	Oral Solution fasted	Capsules fed	Oral Solution fasted	Capsules fed
C _{max} (ng/mL)	544 ± 213*	302 ± 119	622 ± 116	504 ± 132
T _{max} (hours)	2.2 ± 0.8	5 ± 0.8	3.5 ± 1.2	5 ± 1
AUC _{0-24h} (ng·h/mL)	4505 ± 1670	2682 ± 1084	9552 ± 1835	7293 ± 2144

* mean ± standard deviation

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following intravenous administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3–18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 mL/minute following intravenous administration. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions for more information.)

Special Populations

Pediatrics

The pharmacokinetics of SPORANOX[®] Oral Solution were studied in 26 pediatric patients requiring systemic antifungal therapy. Patients were stratified by age: 6 months to 2 years (n=8), 2 to 5 years (n=7) and 5 to 12 years (n=11), and received itraconazole oral solution 5 mg/kg once daily for 14 days. Pharmacokinetic parameters at steady-state (Day 14) were not significantly different among the age strata and are summarized in the table below for all 26 patients:

	Itraconazole	Hydroxyitraconazole
C _{max} (ng/mL)	582.5 ± 382.4*	692.4 ± 355.0
C _{min} (ng/mL)	187.5 ± 161.4	403.8 ± 336.1
AUC _{0-24h} (ng·h/mL)	7706.7 ± 5245.2	13356.4 ± 8942.4
t _{1/2} (hours)	35.8 ± 35.6	17.7 ± 13.0

* mean ± standard deviation

Renal Insufficiency

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 m², 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 AUC₀₋₈). Plasma concentration-versus-time profiles showed wide intersubject variation in all three

groups. Caution should be exercised when the drug is administered in this patient population. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency

Itraconazole is predominantly metabolized in the liver. Patients with impaired hepatic function should be carefully monitored when taking itraconazole. A pharmacokinetic study using a single oral 100 mg capsule dose of itraconazole was conducted in 6 healthy and 12 cirrhotic subjects. 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. The prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. Data are not available in cirrhotic patients during long-term use of itraconazole. (See BOX WARNING, 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 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.

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.

Activity *In Vitro* and *In Vivo*

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

Aspergillus flavus

Aspergillus fumigatus

Blastomyces dermatitidis

Candida albicans

Histoplasma capsulatum

Histoplasma duboisii

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) 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

Pathogen	Broth Microdilution MIC* (µg/mL) at 48 Hours		
	S	I	R
<i>Candida albicans</i>	≤ 0.125	0.25 – 0.5	≥ 1

* A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. The *intermediate* category implies that an infection due to the isolate may be appropriately treated in the body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. The *resistant* category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies. The *intermediate* category is sometimes called *Susceptible-Dose Dependent* (SDD) and both categories are equivalent for itraconazole.

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

QC Strain	Broth Microdilution MIC (µg/mL) at 48 Hours
<i>Candida parapsilosis</i> ATCC* 22019	0.06–0.25
<i>Candida krusei</i> ATCC 6258	0.12–0.5

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

Activity in Animal Models

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis*, *Histoplasma duboisii*, *Aspergillus fumigatus*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*.

Itraconazole administered at 2.5 mg/kg and 5 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and in immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other *Candida* species.

Resistance

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged 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. The relevance of these *in vitro* susceptibility data to clinical outcome remains to be elucidated.

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.

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 ¹⁴C-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.

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 WARNINGS, PRECAUTIONS: Drug Interactions-Calcium Channel Blockers, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations.)

Drug Interactions

Concomitant administration of SPORANOX[®] (itraconazole) Capsules or Oral Solution and certain drugs metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events. Cisapride, oral midazolam, nisoldipine, felodipine, pimozide, quinidine, dofetilide, triazolam, methadone and levacetylmethadol (levomethadyl) are contraindicated with SPORANOX[®]. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, are also contraindicated with SPORANOX[®]. Ergot alkaloids metabolized by CYP3A4 such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylethergometrine (methylethergonovine) are contraindicated with SPORANOX[®]. (See BOX WARNING, and PRECAUTIONS: Drug Interactions.)

SPORANOX[®] is contraindicated for patients who have shown hypersensitivity to itraconazole or its excipients. There is no information regarding cross-hypersensitivity between itraconazole and otherazole antifungal agents. Caution should be used when prescribing SPORANOX[®] to patients with hypersensitivity to other azoles.

WARNINGS

SPORANOX[®] (itraconazole) Oral Solution and SPORANOX[®] Capsules should not be used interchangeably. 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 pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

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 reinstatement 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 cisapride, pimozide, methadone, levacetylmethadol (levomethadyl), or quinidine concomitantly with SPORANOX[®] and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with SPORANOX[®] is contraindicated. (See BOX 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 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 CLINICAL PHARMACOLOGY: Special Populations, PRECAUTIONS: Drug Interactions, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

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).

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. 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. Liver function monitoring should be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications and should 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.

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 BOX 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 pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings 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.

Drug Interactions

Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, the following drug interactions may occur (See Table 1 below and the drug class subheadings that follow):

1. SPORANOX[®] may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with SPORANOX[®]. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant SPORANOX[®] therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, depending on the dose and duration of treatment, itraconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibitors). This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.
2. Inducers of CYP3A4 may decrease the plasma concentrations of itraconazole. SPORANOX[®] may not be effective in patients concomitantly taking SPORANOX[®] and one of these drugs. Therefore, administration of these drugs with SPORANOX[®] is not recommended.
3. Other inhibitors of CYP3A4 may increase the plasma concentrations of itraconazole. Patients who must take SPORANOX[®] concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of SPORANOX[®].

Table 1: Selected Drugs that Are Predicted to Alter the Plasma Concentration of Itraconazole or Have Their Plasma Concentration Altered by SPORANOX[®]*

Drug plasma concentration increased by itraconazole	
Antiarrhythmics	digoxin, dofetilide, [†] quinidine, [†] disopyramide
Anticoagulants	warfarin
Anticonvulsants	carbamazepine
Antimycobacterials	rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide [†]
Benzodiazepines	alprazolam, diazepam, midazolam, [†] , [‡] triazolam [†]
Calcium Channel Blockers	dihydropyridines (including felodipine [†] and nisoldipine [†]), verapamil
Gastrointestinal Motility Agents	cisapride [†]
HMG CoA-Reductase Inhibitors	atorvastatin, cerivastatin, lovastatin, [†] simvastatin [†]
Immunosuppressants	cyclosporine, tacrolimus, sirolimus
Oral Hypoglycemics	oral hypoglycemics
Protease Inhibitors	indinavir, ritonavir, saquinavir
Other	methadone, [†] levacetylmethadol (levomethadyl), [†] ergot alkaloids, [†] halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, fluticasone, trimetrexate, warfarin, cilostazol, eletriptan, fentanyl

Decrease plasma concentration of itraconazole	
Anticonvulsants	carbamazepine, phenobarbital, phenytoin
Antimycobacterials	isoniazid, rifabutin, rifampin
Gastric Acid Suppressors/Neutralizers	antacids, H ₂ -receptor antagonists, proton pump inhibitors
Reverse Transcriptase Inhibitors	nevirapine
Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

* This list is not all-inclusive.

† Contraindicated with SPORANOX[®] based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)

‡ For information on parenterally administered midazolam, see the Benzodiazepine paragraph below.

Antiarrhythmics

The class IA antiarrhythmic quinidine and class III antiarrhythmic dofetilide are known to prolong the QT interval. Coadministration of quinidine or dofetilide with SPORANOX[®] may increase plasma concentrations of quinidine or dofetilide which could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] and quinidine or dofetilide is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

The class IA antiarrhythmic disopyramide has the potential to increase the QT interval at high plasma concentrations. Caution is advised when SPORANOX[®] and disopyramide are administered concomitantly.

Concomitant administration of digoxin and SPORANOX[®] has led to increased plasma concentrations of digoxin via inhibition of P-glycoprotein.

Anticoagulants

SPORANOX[®] enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.

Anticonvulsants

Reduced plasma concentrations of itraconazole were reported when SPORANOX[®] was administered concomitantly with phenytoin. Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of SPORANOX[®] and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, *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.

Antimycobacterials

Drug interaction studies have demonstrated that plasma concentrations of azole antifungal agents and their metabolites, including itraconazole and hydroxyitraconazole, were significantly decreased when these agents were given concomitantly with rifabutin or rifampin. *In vivo* data suggest that rifabutin is metabolized in part by CYP3A4. SPORANOX[®] may inhibit the metabolism of rifabutin. Although no formal study data are available for isoniazid, similar effects should be anticipated. Therefore, the efficacy of SPORANOX[®] could be substantially reduced if given concomitantly with one of these agents. Coadministration is not recommended.

Antineoplastics

SPORANOX[®] may inhibit the metabolism of busulfan, docetaxel, and vinca alkaloids.

Antipsychotics

Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Coadministration of pimozide with SPORANOX[®] could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] and pimozide is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

Benzodiazepines

Concomitant administration of SPORANOX[®] and alprazolam, diazepam, oral midazolam, or triazolam could lead to increased plasma concentrations of these benzodiazepines. Increased plasma concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant administration of SPORANOX[®] and oral midazolam or triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS.) If midazolam is administered parenterally, special precaution and patient monitoring are required since the sedative effect may be prolonged.

Calcium Channel Blockers

Edema has been reported in patients concomitantly receiving SPORANOX[®] and dihydropyridine calcium channel blockers. Appropriate dosage adjustment may be necessary.

Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (e.g., nifedipine, nisoldipine, and felodipine) and verapamil. 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 nisoldipine results in clinically significant increases in nisoldipine plasma concentrations, which cannot be managed by dosage reduction. Therefore the concomitant administration of SPORANOX[®] and nisoldipine is contraindicated. A clinical study showed that felodipine exposure was increased by coadministration of itraconazole, resulting in approximately a 6-fold increase in the AUC and an 8-fold increase in the C_{max}. The concomitant use of SPORANOX[®] and felodipine is contraindicated. (See CONTRAINDICATIONS, WARNINGS, ADVERSE REACTIONS: Post-marketing Experience, and CLINICAL PHARMACOLOGY: Special Populations for more information.)

Gastric Acid Suppressors/Neutralizers

Reduced plasma concentrations of itraconazole were reported when SPORANOX[®] Capsules were administered concomitantly with H₂-receptor antagonists. Studies have shown that absorption of itraconazole is impaired when gastric acid production is decreased. Therefore, SPORANOX[®] should be administered with a cola beverage if the patient has achlorhydria or is taking H₂-receptor antagonists or other gastric acid suppressors. Antacids should be administered at least 1 hour before or 2 hours after administration of SPORANOX[®] Capsules. In a clinical study, when SPORANOX[®] Capsules were administered with omeprazole (a proton pump inhibitor), the bioavailability of itraconazole was significantly reduced. However, as itraconazole is already dissolved in SPORANOX[®] Oral Solution, the effect of H₂-antagonists is expected to be substantially less than with the capsules. Nevertheless, caution is advised when the two drugs are coadministered.

Gastrointestinal Motility Agents

Coadministration of SPORANOX[®] with cisapride can elevate plasma cisapride concentrations which could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] with cisapride is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

HMG CoA-Reductase Inhibitors

Human pharmacokinetic data suggest that SPORANOX[®] inhibits the metabolism of atorvastatin,

cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of SPORANOX[®] with HMG CoA-reductase inhibitors, such as lovastatin or simvastatin is contraindicated. (See CONTRAINDICATIONS and WARNINGS.)

Immunosuppressants

Concomitant administration of SPORANOX[®] and cyclosporine or tacrolimus has led to increased plasma concentrations of these immunosuppressants. Concomitant administration of SPORANOX[®] and sirolimus could increase plasma concentrations of sirolimus.

Macrolide Antibiotics

Erythromycin and clarithromycin are known inhibitors of CYP3A4 (See Table 1) and may increase plasma concentrations of itraconazole. In a small pharmacokinetic study involving HIV infected patients, clarithromycin was shown to increase plasma concentrations of itraconazole. Similarly, following administration of 1 gram of erythromycin ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and AUC_{0-∞} of itraconazole increased by 44% (90% CI: 119–175%) and 36% (90% CI: 108–171%), respectively.

Oral Hypoglycemic Agents

Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when SPORANOX[®] and oral hypoglycemic agents are coadministered.

Polyenes

Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

Protease Inhibitors

Concomitant administration of SPORANOX[®] and protease inhibitors metabolized by CYP3A4, such as indinavir, ritonavir, and saquinavir, may increase plasma concentrations of these protease inhibitors. In addition, concomitant administration of SPORANOX[®] and indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Caution is advised when SPORANOX[®] and protease inhibitors must be given concomitantly.

Reverse Transcriptase Inhibitors

Nevirapine is an inducer of CYP3A4. In vivo studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX[®] and nevirapine is not recommended. In a clinical study, when 8 HIV-infected subjects were treated concomitantly with SPORANOX[®] Capsules 100 mg twice daily and the nucleoside reverse transcriptase inhibitor zidovudine 8 ± 0.4 mg/kg/day, the pharmacokinetics of zidovudine were not affected. Other nucleoside reverse transcriptase inhibitors have not been studied.

Other

- Methadone and levacetylmethadol (levomethadyl) are known to prolong the QT interval and are metabolized by CYP3A4. Co-administration of methadone or levacetylmethadol with SPORANOX[®] could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] and methadone or levacetylmethadol is contraindicated.
- Elevated concentrations of ergot alkaloids can cause ergotism, ie. a risk for vasospasm potentially leading to cerebral ischemia and/or ischemia of the extremities. Concomitant administration of ergot

alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) with SPORANOX[®] is contraindicated.

- Halofantrine has the potential to prolong the QT interval at high plasma concentrations. Caution is advised when SPORANOX[®] and halofantrine are administered concomitantly.
- *In vitro* data suggest that alfentanil is metabolized by CYP3A4. Administration with SPORANOX[®] may increase plasma concentrations of alfentanil.
- Human pharmacokinetic data suggest that concomitant administration of SPORANOX[®] and buspirone results in significant increases in plasma concentrations of buspirone.
- SPORANOX[®] may inhibit the metabolism of certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone.
- *In vitro* data suggest that trimetrexate is extensively metabolized by CYP3A4. *In vitro* animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX[®] and trimetrexate may inhibit the metabolism of trimetrexate.
- Cilostazol and eletriptan are CYP3A4 metabolized drugs that should be used with caution when co-administered with SPORANOX[®].
- Fentanyl plasma concentrations could be increased or prolonged by concomitant use of SPORANOX[®] and may cause potentially fatal respiratory depression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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.

Hydroxypropyl- β -cyclodextrin (HP- β -CD), the solubilizing excipient used in SPORANOX[®] Oral Solution, 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. Development of these tumors may be related to a mitogenic action of cholecystokinin. This finding was not observed in the mouse carcinogenicity study at doses of 500, 2000 or 5000 mg/kg/day for 22–23 months; however, the clinical relevance of these findings is unknown. Based on body surface area comparisons, the exposure to humans of HP- β -CD at the recommended clinical dose of SPORANOX[®] Oral Solution is approximately equivalent to 1.7 times the exposure at the lowest dose in the rat study.

Itraconazole produced no mutagenic effects when assayed in a 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/10T $\frac{1}{2}$ 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).

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). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

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. A pharmacokinetic study was conducted with SPORANOX[®] Oral Solution in 26 pediatric patients, ages 6 months to 12 years, requiring systemic antifungal treatment. Itraconazole was dosed at 5 mg/kg once daily for two weeks and no serious unexpected adverse events were reported. (See CLINICAL PHARMACOLOGY.)

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. No such bone toxicity has been reported in adult patients.

Geriatric Use

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 BOX WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions). Itraconazole should be used with care in elderly patients (see PRECAUTIONS).

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 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. (See CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

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 Event	Itraconazole		Fluconazole (n = 125 [†]) %	Clotrimazole (n = 81 [‡]) %
	Total (n = 350 [*]) %	All controlled studies (n = 272) %		
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
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* 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 Oropharyngeal 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, tremor, and pulmonary infiltration.

Post-marketing Experience

Adverse drug reactions that have been identified during post-approval use of 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.

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, hypokalemia
Nervous system disorders:	Peripheral neuropathy, paresthesia, hypoesthesia, headache, dizziness
Eye disorders:	Visual disturbances, including vision blurred and diplopia
Ear and labyrinth disorders:	Transient or permanent hearing loss, tinnitus
Cardiac disorders:	Congestive heart failure
Respiratory, thoracic and mediastinal disorders:	Pulmonary edema, dyspnea

Gastrointestinal disorders :	Pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhea, constipation, dysgeusia
Hepato-biliary 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, exfoliative dermatitis, leukocytoclastic vasculitis, erythema multiforme, alopecia, photosensitivity, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders :	Myalgia, arthralgia
Renal and urinary disorders :	Urinary incontinence, pollakiuria
Reproductive system and breast disorders :	Menstrual disorders, erectile dysfunction
General disorders and administration site conditions :	Peripheral edema, pyrexia

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, including gastric lavage with sodium bicarbonate, should be employed.

There are limited data on the outcomes of patients ingesting high doses of itraconazole. In patients taking either 1000 mg of SPORANOX[®] (itraconazole) Oral Solution or up to 3000 mg of SPORANOX[®] Capsules, the adverse event profile was similar to that observed at recommended doses.

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 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.

Revised October 2012

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Product of Ireland

Manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

PRINCIPAL DISPLAY PANEL - 150 mL Bottle Label

NDC 50458-295-15

150 mL

SPORANOX[®]
(ITRACONAZOLE)
ORAL SOLUTION

10 mg/mL

Each 1 mL contains:

10 mg of itraconazole in an aqueous solution.

Dosage: For information concerning dosage and

administration of SPORANOX[®] (itraconazole) oral solution, please read accompanying Package Insert.

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

989764

Revised October 2012

Product of Ireland

Manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

janssen

USA - 989764

3 50458-295-15 3

EXP. DATE CONTROL

NDC 50458-295-15 150 mL

SPORANOX[®]
(ITRACONAZOLE)
ORAL SOLUTION

10 mg/mL

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989764
Revised October 2012

Product of Ireland

Manufactured by:
Janssen Pharmaceutica NV
Beerse, Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Rx only

janssen



SPORANOX

itraconazole solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:50458-295
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
itraconazole (itraconazole)	itraconazole	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
HYDROXYPROPYLBETADEX (0.58-0.68 MS)	400 mg in 1 mL
HYDROCHLORIC ACID	
PROPYLENE GLYCOL	
WATER	
SODIUM HYDROXIDE	
SACCHARIN SODIUM	
SORBITOL	
CHERRY	
CAMEL	

Product Characteristics

Color	YELLOW (clear and yellowish)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-295-15	150 mL in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020657	02/21/1997	

Labeler - Janssen Pharmaceuticals, Inc. (063137772)

Establishment			
Name	Address	ID/FEI	Business Operations
Janssen Pharmaceutical		985042969	API MANUFACTURE(50458-295)

Establishment			
Name	Address	ID/FEI	Business Operations
Janssen Pharmaceutica, NV		374747970	API MANUFACTURE(50458-295)

Establishment			
Name	Address	ID/FEI	Business Operations
Janssen Pharmaceutica, NV		370005019	MANUFACTURE(50458-295), ANALYSIS(50458-295)

Revised: 1/2013

Janssen Pharmaceuticals, Inc.