SPORANOX®
(itraconazole)
INJECTION

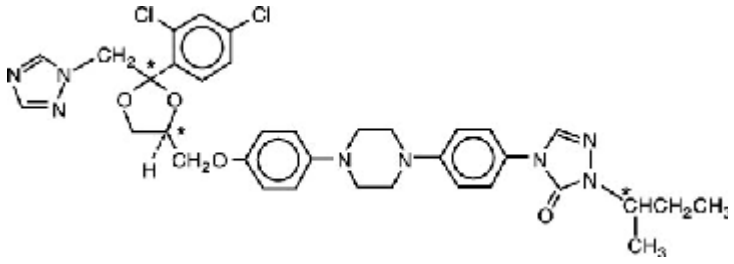
Congestive Heart Failure: When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur during administration of SPORANOX® (itraconazole) Injection, continued SPORANOX® use should be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

Drug Interactions: Coadministration of cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol (levomethadyl) with SPORANOX® (itraconazole) Capsules, Injection 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, levacetylmethadol (levomethadyl), or quinidine concomitantly with SPORANOX® and/or other CYP3A4 inhibitors. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

DESCRIPTION

For intravenous infusion (NOT FOR IV BOLUS INJECTION)

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]-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) Injection is a sterile pyrogen-free clear, colorless to slightly yellow solution for intravenous infusion. Each mL contains 10 mg of itraconazole, solubilized by hydroxypropyl-β-cyclodextrin (400 mg) as a molecular inclusion complex, with 3.8 µL hydrochloric acid, 25 µL propylene glycol, and sodium hydroxide for pH adjustment to 4.5, in water for injection. SPORANOX® Injection is packaged in 25 mL colorless glass ampules, containing 250 mg of itraconazole, contents of which are diluted in 50 mL 0.9% Sodium Chloride Injection, USP (Normal Saline) prior to infusion. When properly administered, contents of one ampule will supply 200 mg of itraconazole.

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 pharmacokinetics of SPORANOX® (itraconazole) Injection (200 mg b.i.d. for two days, then 200 mg q.d. for five days) followed by oral dosing of SPORANOX® Capsules were studied in patients with advanced HIV infection. Steady-state plasma concentrations were reached after the fourth dose for itraconazole and by the seventh dose for hydroxyitraconazole. Steady-state plasma concentrations were maintained by administration of SPORANOX® Capsules, 200 mg b.i.d. Pharmacokinetic parameters for itraconazole and hydroxyitraconazole are presented in the table below:

Parameter	Injection Day 7 n=29		Capsule, 200 mg b.i.d. Day 36 n=12	
	itraconazole	hydroxyitraconazole	itraconazole	hydroxyitraconazole
C_{max} (ng/mL)	2856 ± 866*	1906 ± 612	2010 ± 1420	2614 ± 1703
t_{max} (hr)	1.08 ± 0.14	8.53 ± 6.36	3.92 ± 1.83	5.92 ± 6.14
AUC_{0-12h} (ng•h/mL)	--	--	18768 ± 13933	28516 ± 19149
AUC_{0-24h} (ng•h/mL)	30605 ± 8961	42445 ± 13282	--	--

*mean ± standard deviation

The estimated mean ±SD half-life at steady-state of itraconazole after intravenous infusion was 35.4 ± 29.4 hours. In previous studies, the mean elimination half-life for itraconazole at steady-state after daily oral administration of 100 to 400 mg was 30-40 hours.

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.

Each intravenous dose of 200 mg itraconazole contains 8g hydroxypropyl-β-cyclodextrin to increase the solubility of itraconazole. The pharmacokinetic profiles of each are described below. (See Special Populations–Renal Insufficiency.)

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites. Hydroxyitraconazole, the major metabolite, has *in vitro* antifungal activity comparable to itraconazole. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Based on an oral dose, fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of itraconazole and the active metabolite hydroxyitraconazole account for less than 1% of an intravenous dose. Itraconazole is excreted mainly as inactive metabolites in urine (35%) and feces (54%) within one week of an oral dose. No single excreted metabolite represents more than 5% of a dose. Itraconazole mean total plasma clearance is 278 ± 79 mL/min following intravenous administration. A mean of 89.2% of the administered intravenous dose of hydroxypropyl-β-cyclodextrin is excreted in urine. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions for more information.)

Special Populations

Renal Insufficiency:

A small fraction (<1%) of an intravenous dose of itraconazole is excreted unchanged in urine.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (CrCl 50-79 mL/min), moderate (CrCl 20-49 mL/min), and severe renal impairment (CrCl <20 mL/min) were similar to that in healthy subjects (range of means 42-49 hr vs 48 hr 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 hydroxyitraconazole. (See CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

In patients with normal renal function, the pharmacokinetic profile of hydroxypropyl-β-cyclodextrin, an ingredient of SPORANOX® intravenous formulation, has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority of an 8 g dose of hydroxypropyl-β-cyclodextrin (per 200 mg itraconazole) is eliminated in the urine. Following a single intravenous dose of itraconazole 200 mg, clearance of hydroxypropyl-β-cyclodextrin was reduced in subjects with mild, moderate, and severe renal impairment, resulting in higher exposure to hydroxypropyl-β-cyclodextrin; in these subjects, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropyl-β-cyclodextrin until steady state is reached. Hydroxypropyl-β-cyclodextrin is removed by hemodialysis.

In patients with mild (creatinine clearance 50-80 mL/min) to moderate (creatinine clearance 30-49 mL/min) renal impairment, SPORANOX® Injection should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to SPORANOX® Capsules, if clinically indicated and consistent with approved indications. SPORANOX® Injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). (See CONTRAINDICATIONS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency:

Studies have not been conducted with intravenous itraconazole in patients with hepatic impairment. 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 dose of itraconazole (one 100-mg capsule) 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 SPORANOX® Injection (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® Injection, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX® Injection administration. (See WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

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 exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, Candida albicans*, and *Cryptococcus neoformans*. Itraconazole also exhibits varying

in vitro activity against *Sporothrix schenckii*, *Trichophyton* species, *Candida krusei*, and other *Candida* species.

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.

The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Zygomycete, Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp. Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

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 ^{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.

CLINICAL STUDIES

Empiric Therapy in Febrile Neutropenic Patients:

An open randomized trial compared the efficacy and safety of itraconazole (intravenous followed by oral solution) with amphotericin B for empiric therapy in 384 febrile, neutropenic patients with hematologic malignancies who had suspected fungal infections. Patients received either itraconazole (injection, 200 mg b.i.d. for 2 days followed by 200 mg once daily for up to 14 days, followed by oral solution, 200 mg b.i.d.) or amphotericin B (total daily dose of 0.7-1.0 mg/kg body weight). The longest treatment duration was 28 days. An outcome assignment of "success" required (a) patient survival with resolution of fever and neutropenia within 28 days of treatment, (b) absence of emergent fungal infections, (c) no discontinuation of therapy due to toxicity or lack of efficacy, and (d) treatment for three or more days. The success rate using an intent-to-treat analysis was 47% for the itraconazole group and 38% for the amphotericin B arm.

Overview of Efficacy
(Intent-to-Treat Population)

Efficacy Parameters	**SPORANOX®** N=179 (%)	**Amphotericin B** N=181 (%)
Success	84 (47%)	68 (38%)
Unevaluable*	24 (13%)	44 (24%)
Failure	71 (40%)	69 (38%)
Reason for Failure		
Intolerance after > 3 days of antifungal medication	12	37
Persistent fever	20	7
Change in antifungal medication due to fever	13	1
Emergent fungal infection	10	9
Documented bacterial or viral infection	7	8
Insufficient response	6	5
Deterioration of signs and symptoms	2	0
Death after > 3 days antifungal medication	1	2
Resolution of fever	131 (73%)	127 (70%)
Survival	161 (90%)	156 (86%)

* Treatment duration ≤ 3 days (including patients who died within 3 days, withdrew because of adverse events or were deemed ineligible due to a confirmed pre-treatment infection).

INDICATIONS AND USAGE

SPORANOX® (itraconazole) Injection/Oral Solution is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. (NOTE: In a comparative trial, the overall response rate for itraconazole-treated subjects was higher than for amphotericin B-treated subjects. However, compared to amphotericin B-treated subjects, a larger number of itraconazole-treated subjects discontinued treatment due to persistent fever and a change in antifungal medication due to fever. Whereas, a larger number of amphotericin B-treated subjects discontinued due to drug intolerance. (See CLINICAL STUDIES section.)

SPORANOX® (itraconazole) Injection is also indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Blastomycosis, pulmonary and extrapulmonary;

2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and

3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and

other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

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

CONTRAINDICATIONS

Drug Interactions:

Concomitant administration of SPORANOX® (itraconazole) Capsules, Injection, 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, pimozide, quinidine, dofetilide, triazolam 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 methylergometrine (methylergonovine) 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 other azole antifungal agents. Caution should be used when prescribing SPORANOX® to patients with hypersensitivity to other azoles.

SPORANOX IV cannot be used when administration of Sodium Chloride Injection is contraindicated.

The excipient hydroxypropyl-β-cyclodextrin is eliminated through glomerular filtration. Therefore, SPORANOX IV is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min). (See CLINICAL PHARMACOLOGY: Special Populations, PRECAUTIONS, and DOSAGE and ADMINISTRATION.)

WARNINGS

SPORANOX® (itraconazole) Injection 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 PRECAUTIONS: 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 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 cisapride, pimozide, 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® Injection 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® Injection, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX® Injection 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 SPORANOX® Injection (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.)

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® Injection, the treatment should be discontinued.

Renal Impairment:

As severe renal impairment prolongs the elimination rate of hydroxypropyl-β-cyclodextrin, SPORANOX® (itraconazole) Injection should not be used in patients with severe renal dysfunction (creatinine clearance < 30 mL/min). (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 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:

SPORANOX® Injection 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 PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

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 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 following 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®[1]

Drug plasma concentration increased by itraconazole	
Antiarrhythmics	digoxin, dofetilide,[2] quinidine,[2] disopyramide
Anticonvulsants	Carbamazepine
Antimycobacterials	Rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide[2]
Benzodiazepines	alprazolam, diazepam, midazolam,[2,3] triazolam[2]
Calcium Channel Blockers	dihydropyridines (including nisoldipine[2]), verapamil
Gastrointestinal Motility Agents	cisapride[2]
HMG CoA-Reductase Inhibitors	atorvastatin, cerivastatin, lovastatin,[2] simvastatin[2]
Immunosuppressants	cyclosporine, tacrolimus, sirolimus
Oral Hypoglycemics	oral hypoglycemics
Protease Inhibitors	indinavir, ritonavir, saquinavir
Other	levacetylmethadol (levomethadyl),[2] ergot alkaloids,[2] 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
Reverse Transcriptase Inhibitors	Nevirapine
Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

[1] This list is not all-inclusive.
[2] Contraindicated with SPORANOX® based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)
[3] 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.

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

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 and 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 $_{0-\infty}$ 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:

- Levacetylmethadol (levomethadyl) is known to prolong the QT interval and is metabolized by CYP3A4. Co-administration of levacetylmethadol with SPORANOX® could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX® and 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®.
- SPORANOX® enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.
- 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® Injection and 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. The relevance of the findings with orally administered HP-β-CD to potential carcinogenic effects for SPORANOX® Injection is uncertain.

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/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).

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 for the treatment of systemic fungal infections 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. No pharmacokinetic data on SPORANOX® Capsules or Injection are available in children. A small number of patients ages 3 to 16 years have been treated with 100 mg/day of itraconazole capsules for systemic fungal infections, and no serious unexpected adverse effects have been reported. SPORANOX® Oral Solution (5 mg/kg/day) has been administered to pediatric patients (N=26, ages 6 months to 12 years) for 2 weeks and no serious unexpected adverse events were reported.

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:

Clinical studies of SPORANOX® Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, 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 BOX WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions). Itraconazole should be used with care in elderly patients (see PRECAUTIONS).

Renal Impairment:

Hydroxypropyl-β-cyclodextrin, when administered intravenously, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment defined as creatinine clearance below 30 mL/min, SPORANOX IV is contraindicated (see CONTRAINDICATIONS).

In patients with mild (defined as creatinine clearance 50-80 mL/min) and moderate (defined as creatinine clearance 30-49 mL/min) renal impairment, SPORANOX IV should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to modifying the antifungal regimen to an alternate medication with similar antimycotic coverage. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, and DOSAGE and ADMINISTRATION for further information.).

Hepatic Impairment:

Studies have not been conducted with intravenous itraconazole 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 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: General and Information for Patients.)

Adverse Events Reported in Trials in Patients with SPORANOX® Injection

Adverse events considered at least possibly drug related are shown in Table 2 and are based on the experience of 360 patients treated with SPORANOX® Injection in four pharmacokinetic, one uncontrolled and four active controlled studies where the control was amphotericin B or fluconazole. Nearly all patients were neutropenic or were otherwise immunocompromised and were treated empirically for febrile episodes, for documented systemic fungal infections, or in trials to determine pharmacokinetics. The dose of SPORANOX® Injection was 200 mg twice daily for the first two days followed by a single daily dose of 200 mg for the remainder of the intravenous treatment period. The majority of patients received between 7 and 14 days of SPORANOX® Injection.

Table 2 Summary of Possibly or Definitely Drug-Related Adverse Events Reported by ≥2% of Subjects

Adverse Event	Total SPORANOX® Injection (N=360) %	Comparative Studies		
		SPORANOX® Injection (N=234) %	Intravenous Fluconazole (N=32) %	Intravenous Amphotericin B (N=202) %
Gastrointestinal system disorders				
Nausea	8	9	0	15
Diarrhea	6	6	3	9
Vomiting	4	6	0	10
Abdominal pain	2	2	0	3
Constipation	0	1	3	0
Metabolic and nutritional disorders				
Hypokalemia	5	8	0	29
Alkaline phosphatase increased	1	2	3	2
Serum creatinine increased	2	2	3	26
Hypomagnesemia	1	1	0	5
Blood urea nitrogen increased	0	1	0	7
Fluid overload	0	0	0	3
Hypocalcemia	0	0	0	3
Liver and biliary system disorders				
Bilirubinemia	4	6	9	3
SGPT/ALT Increased	2	3	3	1
Hepatic function abnormal	1	2	0	2
Jaundice	1	2	0	0
SGOT/AST increased	1	2	0	0
Body as a whole – General disorders				
Pain	1	2	0	0
Rigors	0	0	0	34
Fever	0	0	0	6
Skin and appendages disorders				
Rash	3	3	3	3
Sweating increased	1	2	0	0
Respiratory system disorder				
Dyspnea	0	0	0	3
Central and peripheral nervous system disorders				
Dizziness	1	2	0	1
Headache	2	2	0	3
Urinary system disorders				
Renal function abnormal	1	1	0	11
Application site disorder				
Application site reaction	4	0	0	0
Cardiovascular disorders, general				
Hypotension	0	0	0	3
Hypertension	0	0	0	2
Heart rate and rhythm disorders				
Tachycardia	0	1	0	3
Vascular (extracardiac) disorders				
Vein disorder	3	0	0	0

The following adverse events occurred in less than 2% of patients in clinical trials of SPORANOX® Injection: LDH increased, edema, albuminuria, hyperglycemia, and hepatitis.

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
Gastrointestinal disorders:	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, 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

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.

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, or b.i.d. dosing for four days with SPORANOX® Injection, the adverse event profile was similar to that observed at recommended doses.

DOSAGE AND ADMINISTRATION

Use only the components [SPORANOX® (itraconazole) Injection ampule, 0.9% Sodium Chloride Injection, USP (Normal Saline) bag and filtered infusion set] provided in the kit: **DO NOT SUBSTITUTE**.

SPORANOX® Injection should not be diluted with 5% Dextrose Injection, USP, or with Lactated Ringer's Injection, USP, alone or in combination with any other diluent. The compatibility of SPORANOX® Injection with diluents other than 0.9% Sodium Chloride Injection, USP (Normal Saline) is not known. **NOT FOR IV BOLUS INJECTION.**

NOTE: After reconstitution, the diluted SPORANOX® Injection may be stored refrigerated (2-8°C) or at room temperature (15-25°C) for up to 48 hours, when protected from direct light. During administration, exposure to normal room light is acceptable.

NOTE: Use only a dedicated infusion line for administration of SPORANOX® Injection. Do not introduce concomitant medication in the same bag nor through the same line as SPORANOX® Injection. Other medications may be administered after flushing the line/catheter with 0.9% Sodium Chloride Injection, USP, as described below, and removing and replacing the entire infusion line. Alternatively, utilize another lumen, in the case of a multi-lumen catheter.

Correct preparation and administration of SPORANOX® Injection are necessary to ensure maximal efficacy and safety. A precise mixing ratio is required in order to obtain a stable admixture. It is critical to maintain a 3.33 mg/mL itraconazole:diluent ratio. Failure to maintain this concentration will lead to the formation of a precipitate.

Add the full contents (25 mL) of the SPORANOX® Injection ampule into the infusion bag provided, which contains 50 mL of 0.9% Sodium Chloride Injection, USP (Normal Saline). Mix gently after the solution is completely transferred. Withdraw and discard 15 mL of the solution before administering to the patient. Using a flow control device, infuse 60 mL of the dilute solution (3.33 mg/mL = 200 mg itraconazole, pH apx. 4.8) intravenously over 60 minutes, using an extension line and the infusion set provided. After administration, flush the infusion set with 15-20 mL of 0.9% Sodium Chloride Injection, USP, over 30 seconds-15 minutes, via the two-way stopcock. Do not use Bacteriostatic Sodium Chloride Injection, USP. The compatibility of SPORANOX® Injection with flush solutions other than 0.9% Sodium Chloride Injection, USP (Normal Saline) is not known. Discard the entire infusion line.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Empiric Therapy in Febrile, Neutropenic Patients with Suspected Fungal Infections (ETFN):

The recommended dose of SPORANOX® Injection is 200 mg b.i.d. for four doses, followed by 200 mg once daily for up to 14 days. Each intravenous dose should be infused over 1 hour. Treatment should be continued with SPORANOX® Oral Solution 200 mg (20 mL) b.i.d. until resolution of clinically significant neutropenia. The safety and efficacy of SPORANOX® use exceeding 28 days in ETFN is not known.

Treatment of Blastomycosis, Histoplasmosis and Aspergillosis:

The recommended intravenous dose is 200 mg b.i.d. for four doses, followed by 200 mg q.d. Each intravenous dose should be infused over 1 hour.

For the treatment of blastomycosis, histoplasmosis and aspergillosis, SPORANOX® can be given as oral capsules or intravenously. The safety and efficacy of SPORANOX® Injection administered for greater than 14 days is not known.

Total itraconazole therapy (SPORANOX® Injection followed by SPORANOX® Capsules) should be continued for a minimum of 3 months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Use in Patients with Renal Impairment:

Limited data are available on the use of intravenous itraconazole in patients with renal impairment.

Hydroxypropyl-β-cyclodextrin, a required component of SPORANOX® intravenous formulation, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min), the use of SPORANOX® IV is contraindicated. (See CONTRAINDICATIONS.)

In patients with mild (defined as creatinine clearance 50-80 mL/min) to moderate (defined as creatinine clearance 30-49 mL/min) renal impairment, SPORANOX® IV should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to SPORANOX® capsules. (see CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, and PRECAUTIONS.)

Use in Patients with Hepatic Impairment:

Limited data are available on the use of 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) Injection for intravenous infusion is supplied as a kit (NDC 50458-298-01), containing one 25 mL colorless glass ampule of itraconazole 10 mg/mL sterile, pyrogen-free solution (NDC 50458-297-10), one 50 mL bag (100 mL capacity) of 0.9% Sodium Chloride Injection, USP (Normal Saline) and one filtered infusion set.

Store at or below 25°C (77°F). Protect from light and freezing.

Keep out of reach of children.

SPORANOX®
(ITRACONAZOLE)
INJECTION

Manufactured for:
Ortho Biotech Products, L.P
Raritan, NJ 08869

Manufactured by:
Hospira, Inc.
Lake Forest, IL 60045

TBD

U.S. Patent 4,727,064

TBD
Revised TBD