CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

FINAL PRINTED LABELING

SPORANOX® (itraconazole) INJECTION

WARNING: Coadministration of terfenadine, astemizole, and cisapride with SPORANOX® (itraconazole) Capsules, Oral Solution or Injection is contraindicated. SPORANOX® is a potent inhibitor of the cytochrome P450 3A4 enzyme system and may raise plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including death, ventricular tachycardia, and torsades de pointes have occurred in patients taking itraconazole concomitantly with terfenadine or cisapride, which are metabolized by the cytochrome P450 3A4 system. 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:

[chemical structure]

(±)-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® 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		Capsules, 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. Approximately 93-101% of hydroxypropyl β cyclodextrin was excreted unchanged in the urine within 12 hours after dosing.

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 extensively metabolized 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/min following intravenous administration. Approximately 80-90% of hydroxypropyl-β-cyclodextrin is eliminated through the kidneys.

Special populations:

Renal Insufficiency: Plasma concentrations of itraconazole in patients with mild to moderate renal insufficiency were comparable to those obtained in healthy subjects. The majority of the 8-gram dose of hydroxypropyl-β-cyclodextrin was eliminated in the urine during the 120-hour collection period in normal subjects and in patients with mild to severe renal insufficiency. Following a single intravenous dose of 200 mg to subjects with severe renal impairment (creatinine clearance ≤ 19 mL/minute), clearance of hydroxypropyl-β-cyclodextrin was reduced six-fold compared with subjects with normal renal function. SPORANOX® Injection should not be used in patients with creatinine clearance < 30 mL/min.

Hepatic Insufficiency: The effect of hepatic impairment on plasma concentrations of itraconazole is unknown. It is recommended that patients with hepatic impairment be carefully monitored when taking itraconazole.

MICROBIOLOGY

Mechanism of Action: *In vitro* studies have demonstrated that itraconazole inhibits the cytochrome P-450-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 spp., *Candida krusei* and other Candida spp. The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Correlation between *in vitro* minimum inhibitory concentration (MIC) results 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 5.0 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 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 upon 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.

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.

INDICATIONS AND USAGE

SPORANOX® (itraconazole) Injection is 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.

CONTRAINDICATIONS

Coadministration of SPORANOX® (itraconazole) Capsules, Oral Solution or Injection with certain drugs metabolized by the P450 3A4 enzyme system may result in increased plasma concentrations of those drugs leading to potentially serious and/or life-threatening adverse events. Terfenadine, astemizole, triazolam, oral midazolam and cisapride are specifically contraindicated with SPORANOX®. HMG-CoA reductase inhibitors metabolized by this system (e.g., lovastatin and simvastatin) should also be discontinued during SPORANOX® therapy. (See PRECAUTIONS: Drug Interactions.)

SPORANOX® is contraindicated in patients who have shown hypersensitivity to the drug or its excipients. There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX® to patients with hypersensitivity to other azoles.

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.)

Hepatitis: There have been rare cases of reversible idiosyncratic hepatitis reported among patients taking SPORANOX® Capsules. SPORANOX® has been associated with rare cases of serious hepatotoxicity, including fatalities, primarily in patients with serious underlying medical conditions taking multiple medications. The causal association with SPORANOX® is uncertain. If clinical signs and symptoms develop that are consistent with liver disease and may be attributable to itraconazole, SPORANOX® should be discontinued.

Cardiac Dysrhythmias: There have been rare cases of life-threatening cardiac dysrhythmia and death reported in patients receiving terfenadine and itraconazole. Coadministration of terfenadine, astemizole and cisapride with SPORANOX® is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

PRECAUTIONS

General: Hepatic enzyme test values should be monitored in patients with preexisting hepatic functions abnormalities. Hepatic enzyme test values should be monitored at any time a patient develops signs or symptoms suggestive of liver dysfunction.
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.*)

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.)

Drug interactions: Both itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of the cytochrome P450 3A4 enzyme system. Coadministration of SPORANOX® and drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. Therefore, unless otherwise specified, concomitant medications metabolized by the P450 3A4 enzyme system should be discontinued as medically indicated.

Table of Selected Drugs That Are Predicted to Have Plasma Concentrations Increased by Itraconazole*

Anticoagulants: warfarin
Antihistamines: terfenadine*, astemizole*
Anti-HIV protease inhibitors: ritonavir, indinavir
Antineoplastic agents: vinca alkaloids, busulfan
Benzodiazepines: midazolam*†, triazolam*, diazepam
Calcium channel blockers: dihydropyridines
Cholesterol-lowering agents: lovastatin*, simvastatin*
GI motility agents: cisapride*
Immunosuppressive agents: cyclosporine, tacrolimus
Steroids: methylprednisolone
Other: digoxin, quinidine

*This table is not all inclusive.
*Specifically contraindicated with SPORANOX® based on clinical and/or pharmacokinetics studies (see WARNINGS and below).
†See paragraph below on *Benzodiazepines* for information on parenteral administration.

Table of Selected Drugs That Are Predicted to Decrease Itraconazole Plasma Concentrations*‡

Anticonvulsants: phenytoin, phenobarbital, carbamazepine
Antimycobacterial agents: isoniazid, rifampin, rifabutin

*This table is not all inclusive.
‡SPORANOX® may not be effective due to decreased itraconazole plasma concentrations in patients using these agents concomitantly.

Anticoagulants: It has been reported that SPORANOX® enhances the anticoagulant effect of coumarin-like drugs. Therefore, prothrombin time should be carefully monitored in patients receiving SPORANOX® and coumarin-like drugs simultaneously.

Anticonvulsants: Reduced plasma concentrations of itraconazole were reported when SPORANOX® was coadministered with phenytoin. The physician is advised to monitor the plasma concentrations of itraconazole when phenytoin is taken concurrently, and to increase the dose of SPORANOX® if necessary.

Antihistamines: Coadministration of terfenadine with SPORANOX® has led to elevated plasma concentrations of terfenadine, resulting in rare instances of life-threatening cardiac dysrhythmia and death. Coadministration of astemizole with SPORANOX® has led to elevated plasma concentrations of astemizole and desmethylastemizole which

may prolong the QT intervals. Therefore, concomitant administration of SPORANOX® with astemizole is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

Anti-HIV protease inhibitors: Coadministration of SPORANOX® with protease inhibitors primarily metabolized by the cytochrome P450 3A4 enzyme system, such as ritonavir or indinavir, may result in changes in plasma concentrations of both drugs. Caution is advised when these drugs are used concomitantly.

Anti-HIV reverse transcriptase inhibitors: The results from a study in which eight HIV-infected individuals were treated with zidovudine, 8 ± 0.4 mg/kg/day, showed that the pharmacokinetics of zidovudine were not affected during concomitant administration of SPORANOX® Capsules, 100 mg b.i.d. Other agents have not been studied.

Antimycobacterial agents: Plasma concentrations of azole antifungal agents are reduced when given concurrently with isoniazid or rifampin. Alternative antifungal therapy should be considered if rifampin or isoniazid therapy is necessary. A similar effect may be expected with rifabutin.

Antineoplastic agents: The metabolism of vinca alkaloids may be inhibited by itraconazole. Therefore, patients receiving SPORANOX® concomitantly with vinca alkaloids should be monitored for an increase and/or prolongation of the effects of the latter drug product, including adverse effects such as peripheral neuropathy and ileus, and the dose of the vinca alkaloid should be adjusted appropriately. Increased plasma concentrations of busulfan have been reported with coadministration of SPORANOX®.

Benzodiazepines: Coadministration of SPORANOX® with oral midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects. These agents should not be used

in patients treated with SPORANOX®. If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged. (See CONTRAINDICATIONS.)

Calcium channel blockers: Edema has been reported in patients concomitantly receiving SPORANOX® and dihydropyridine calcium channel blockers. Appropriate dosage adjustments may be necessary.

Cholesterol-lowering agents: Human pharmacokinetic data indicate that SPORANOX® inhibits the metabolism of lovastatin resulting in significantly elevated plasma concentrations of lovastatin or lovastatin acid, which have been associated with rhabdomyolysis. Use of HMG-CoA reductase inhibitors metabolized by the P450 3A4 enzyme system, such as lovastatin or simvastatin, should be temporarily discontinued during SPORANOX® therapy. (See CONTRAINDICATIONS.)

Digoxin: Coadministration of SPORANOX® and digoxin has led to increased plasma concentrations of digoxin. Digoxin concentrations should be monitored at the initiation of SPORANOX® therapy and frequently thereafter, and the dose of digoxin should be adjusted appropriately.

GI motility agents: Human pharmacokinetic data indicate that oral ketoconazole potently inhibits the metabolism of cisapride resulting in significantly elevated plasma concentrations of cisapride. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. *In vitro* data suggest that itraconazole also markedly inhibits the biotransformation system mainly responsible for the metabolism of cisapride; therefore, concomitant administration of SPORANOX® with cisapride is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

Immunosuppressive agents: Coadministration of SPORANOX® and cyclosporine or tacrolimus has led to increased plasma concentrations of the latter two agents. Cyclosporine and tacrolimus concentrations should be monitored at the initiation of SPORANOX® therapy and frequently thereafter, and the dose of cyclosporine or tacrolimus should be adjusted appropriately.

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.

Quinidine: Tinnitus and decreased hearing have been reported in patients concomitantly receiving SPORANOX® and quinidine.

Steroids: The metabolism of methylprednisolone may be inhibited by itraconazole. Therefore, patients receiving SPORANOX® concomitantly with methylprednisolone should be monitored for an increase and/or prolongation of the effects of the latter drug product, including adverse effects, and the dose of methylprednisolone should be adjusted appropriately.

Polyenes: Prior treatment with itraconazole, as with 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. (see MICROBIOLOGY: Resistance.)

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. The relevance of the findings with orally administered HP-β-CD to potential carcinogenic effects for SPORANOX® (itraconazole) 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* (six 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.

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 capsules or injection are available in children. A small number of patients age 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, age 0.5-12 years) for two weeks and no serious unexpected adverse events were reported.

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 one year or 160 mg/kg/day (20x MRHD) for six months, itraconazole induced small tooth pulp with hypocellular appearance in some rats. While no such bone toxicity has been reported in adult patients, the long term effect of itraconazole in pediatric patients is unknown.

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.

ADVERSE REACTIONS

There have been rare cases of reversible idiosyncratic hepatitis reported among patients taking SPORANOX® (itraconazole) Capsules. SPORANOX® has been associated with rare cases of serious hepatotoxicity, including fatalities, primarily in patients with serious underlying medical conditions taking multiple medications. The causal association with SPORANOX® is uncertain. If clinical signs and symptoms develop that are consistent with liver disease and may be attributable to itraconazole, SPORANOX® should be discontinued. (See WARNINGS.)

Adverse events considered at least possibly drug related are listed below 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.

SUMMARY OF POSSIBLY OR DEFINITELY DRUG-RELATED ADVERSE EVENTS REPORTED BY ≥1% OF SPORANOX® INJECTION PATIENTS (TOTAL)				
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
Metabolic and nutritional disorders				
Hypokalemia	5	8	0	29
Alkaline phosphatase inc.	1	2	3	2
BUN increased	2	2	3	26
Hypomagnesemia	1	1	0	5
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	1
SGOT/AST increased	1	2	0	1
Body as a whole – General disorders				
Pain	1	2	0	1
Edema	1	1	0	1
Skin and appendages disorders				
Rash	3	3	3	3
Sweating increased	1	2	0	1
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
Albuminuria	1	0	0	0
Application site disorder				
Application site reaction	4	0	0	0
Vascular (extracardiac) disorders				
Vein disorder	3	0	0	0

The following adverse events occurred in less than 1% of patients in clinical trials of SPORANOX® Injection: constipation, hyperglycemia, hepatitis, fever, rigors, dyspnea, and hypotension.

In worldwide postmarketing experience with SPORANOX® Capsules, allergic reactions including rash, pruritus, urticaria, angioedema and in rare instances, anaphylaxis and Stevens-Johnson syndrome, have been reported. Post-marketing experiences have also included reports of elevated liver enzymes and rare hepatitis. Although the causal association with SPORANOX® is uncertain, rare alopecia, hypertriglyceridemia, neutropenia and isolated cases of neuropathy have also been reported.

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, 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.

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. 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. 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.

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.

SPORANOX® Injection should not be used in patients with creatinine clearance <30 mL/min.

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.

U.S. Patent 4,267,179
DATE: March 1999
JANSSEN PHARMACEUTICA
Titusville, NJ 08560

Distributed by:
ORTHO BIOTECH INC.
Raritan, NJ 08869
Manufactured by:
Abbott Laboratories, Inc.
North Chicago, IL 60064