

JANSSEN
PHARMACEUTICA
PRODUCTS, L.P.

SPORANOX[®]
(ITRACONAZOLE)
CAPSULES

Congestive Heart Failure

SPORANOX[®] (itraconazole) Capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. If signs or symptoms of congestive heart failure occur during administration of SPORANOX[®] Capsules, discontinue administration. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. (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, or dofetilide 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, 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:

(insert 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]-Ä²-1,2,4-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]-Ä²-1,2,4-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]-Ä²-1,2,4-triazolin-5-one

Itraconazole has a molecular formula of C₃₅H₃₈Cl₂N₈O₄ 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[®] Capsules contain 100 mg of itraconazole coated on sugar spheres. Inactive ingredients are gelatin, hydroxypropyl methylcellulose, polyethylene glycol (PEG) 20,000, starch, sucrose, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22 and D&C Red No. 28.

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 are approximately 3.3 times higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See MICROBIOLOGY.)

The pharmacokinetics of itraconazole after intravenous administration and its absolute oral bioavailability from an oral solution were studied in a randomized crossover study in 6 healthy male volunteers. The observed absolute oral bioavailability of itraconazole was 55%.

The oral bioavailability of itraconazole is maximal when SPORANOX[®] (itraconazole) Capsules are taken with a full meal. The pharmacokinetics of itraconazole were studied in 6 healthy male volunteers who received, in a crossover design, single 100-mg doses of itraconazole as a polyethylene glycol capsule, with or without a full meal. The same 6 volunteers also received 50 mg or 200 mg with a full meal in a crossover design. In this study, only itraconazole plasma concentrations were measured. The respective pharmacokinetic parameters for itraconazole are presented in the table below:

	50 mg (fed)	100 mg (fed)	100 mg (fasted)	200 mg (fed)
C _{max} (ng/mL)	45 ± 16*	132 ± 67	38 ± 20	289 ± 100
T _{max} (hours)	3.2 ± 1.3	4.0 ± 1.1	3.3 ± 1.0	4.7 ± 1.4
AUC _{0-∞} (ng·h/mL)	567 ± 264	1899 ± 838	722 ± 289	5211 ± 2116

*mean ± standard deviation

Doubling the SPORANOX[®] dose results in approximately a three-fold increase in the itraconazole plasma concentrations.

Values given in the table below represent data from a crossover pharmacokinetics study in which 27 healthy male volunteers each took a single 200-mg dose of SPORANOX[®] Capsules with or without a full meal:

	Itraconazole		Hydroxyitraconazole	
	Fed	Fasted	Fed	Fasted
C _{max} (ng/mL)	239 ± 85*	140 ± 65	397 ± 103	286 ± 101
T _{max} (hours)	4.5 ± 1.1	3.9 ± 1.0	5.1 ± 1.6	4.5 ± 1.1
AUC _{0-∞} (ng·h/mL)	3423 ± 1154	2094 ± 905	7978 ± 2648	5191 ± 2489
t _{1/2} (hours)	21 ± 5	21 ± 7	12 ± 3	12 ± 3

*mean ± standard deviation

Absorption of itraconazole under fasted conditions in individuals with relative or absolute achlorhydria, such as patients with AIDS or volunteers taking gastric acid secretion suppressors (e.g., H₂ receptor antagonists), was increased when SPORANOX[®] Capsules were administered with a cola beverage. Eighteen men with AIDS received single 200-mg doses of SPORANOX[®] Capsules under fasted conditions with 8 ounces of water or 8 ounces of a cola beverage in a crossover design. The absorption of itraconazole was increased when SPORANOX[®] Capsules were coadministered with a cola beverage, with AUC₀₋₂₄ and C_{max} increasing 75% ± 121% and 95% ± 128%, respectively.

Thirty healthy men received single 200-mg doses of SPORANOX[®] Capsules under fasted conditions either 1) with water; 2) with water, after ranitidine 150 mg b.i.d. for 3 days; or 3) with cola, after ranitidine 150 mg b.i.d. for 3 days. When SPORANOX[®] Capsules were administered after ranitidine pretreatment, itraconazole was absorbed to a lesser extent than when SPORANOX[®] Capsules were administered alone, with decreases in AUC₀₋₂₄ and C_{max} of 39% ± 37% and 42% ± 39%, respectively. When SPORANOX[®] Capsules were administered with cola after ranitidine pretreatment, itraconazole absorption was comparable to that observed when SPORANOX[®] Capsules were administered alone. (See PRECAUTIONS: Drug Interactions.)

Steady-state concentrations were reached within 15 days following oral doses of 50 mg to 400 mg daily. Values given in the table below are data at steady-state from a pharmacokinetics study in which 27 healthy male volunteers took 200-mg SPORANOX[®] Capsules b.i.d.(with a full meal) for 15 days:

	Itraconazole	Hydroxyitraconazole
C _{max} (ng/mL)	2282 ± 514*	3488 ± 742
C _{min} (ng/mL)	1855 ± 535	3349 ± 761
T _{max} (hours)	4.6 ± 1.8	3.4 ± 3.4
AUC _{0-12 h} (ng·h/mL)	22569 ± 5375	38572 ± 8450
t _{1/2} (hours)	64 ± 32	56 ± 24

*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 liters.

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:

Renal Insufficiency: 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. x 1.73 m², the bioavailability 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.

Hepatic Insufficiency: A pharmacokinetic study using a single 100-mg dose of itraconazole (one 100-mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC were seen between these two groups. A statistically significant reduction in mean C_{max} (47%) and a twofold increase in the elimination half-life (37 ± 17 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

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[®] Capsules, SPORANOX[®] should be discontinued. (See CONTRAINDICATIONS, 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. The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. 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.

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.

INDICATIONS AND USAGE

SPORANOX[®] (itraconazole) Capsules are 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 before 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, antiinfective therapy should be adjusted accordingly.

SPORANOX[®] Capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:

1. Onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium), and
2. Onychomycosis of the fingernail due to dermatophytes (tinea unguium).

Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of

onychomycosis.

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

Description of Clinical Studies:

Blastomycosis: Analyses were conducted on data from two open-label, non-concurrently controlled studies (N=73 combined) in patients with normal or abnormal immune status. The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first 2 weeks, and all signs and symptoms cleared between 3 and 6 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole for the treatment of blastomycosis compared with the natural history of untreated cases.

Histoplasmosis: Analyses were conducted on data from two open-label, non-concurrently controlled studies (N=34 combined) in patients with normal or abnormal immune status (not including HIV-infected patients). The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first 2 weeks, and all signs and symptoms cleared between 3 and 12 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole for the treatment of histoplasmosis, compared with the natural history of untreated cases.

Histoplasmosis in HIV-infected patients: Data from a small number of HIV-infected patients suggested that the response rate of histoplasmosis in HIV-infected patients is similar to that of non-HIV-infected patients. The clinical course of histoplasmosis in HIV-infected patients is more severe and usually requires maintenance therapy to prevent relapse.

Aspergillosis: Analyses were conducted on data from an open-label, “single-patient-use” protocol designed to make itraconazole available in the U.S. for patients who either failed or were intolerant of amphotericin B therapy (N=190). The findings were corroborated by two smaller open-label studies (N=31 combined) in the same patient population. Most adult patients were treated with a daily dose of 200 to 400 mg, with a median duration of 3 months. Results of these studies demonstrated substantial evidence of effectiveness of

itraconazole as a second-line therapy for the treatment of aspergillosis compared with the natural history of the disease in patients who either failed or were intolerant of amphotericin B therapy.

Onychomycosis of the toenail: Analyses were conducted on data from three double-blind, placebo-controlled studies (N=214 total; 110 given SPORANOX[®] Capsules) in which patients with onychomycosis of the toenails received 200 mg of SPORANOX[®] Capsules once daily for 12 consecutive weeks. Results of these studies demonstrated mycologic cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 54% of patients. Thirty-five percent (35%) of patients were considered an overall success (mycologic cure plus clear or minimal nail involvement with significantly decreased signs) and 14% of patients demonstrated mycologic cure plus clinical cure (clearance of all signs, with or without residual nail deformity). The mean time to overall success was approximately 10 months. Twenty-one percent (21%) of the overall success group had a relapse (worsening of the global score or conversion of KOH or culture from negative to positive).

Onychomycosis of the fingernail: Analyses were conducted on data from a double-blind, placebo-controlled study (N=73 total; 37 given SPORANOX[®] Capsules) in which patients with onychomycosis of the fingernails received a 1-week course (pulse) of 200 mg of SPORANOX[®] Capsules b.i.d., followed by a 3-week period without SPORANOX[®], which was followed by a second 1-week pulse of 200 mg of SPORANOX[®] Capsules b.i.d. Results demonstrated mycologic cure in 61% of patients. Fifty-six percent (56%) of patients were considered an overall success and 47% of patients demonstrated mycologic cure plus clinical cure. The mean time to overall success was approximately 5 months. None of the patients who achieved overall success relapsed.

CONTRAINDICATIONS

Congestive Heart Failure: SPORANOX[®] (itraconazole) Capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, PRECAUTIONS: Drug Interactions-Calcium Channel Blockers, and ADVERSE REACTIONS: Post-marketing Experience.)

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, pimozide, quinidine, dofetilide, and triazolam are contraindicated with SPORANOX[®]. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, are also contraindicated with SPORANOX[®]. (See BOX WARNING, and PRECAUTIONS: Drug Interactions.)

SPORANOX[®] should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy.

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.

WARNINGS

SPORANOX[®] (itraconazole) Capsules and SPORANOX[®] Oral Solution should not be used interchangeably. This is because drug exposure is greater with the Oral Solution than with the Capsules when the same dose of drug is given. In addition, the topical effects of mucosal exposure may be different between the two formulations. Only the Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis.

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. If clinical signs or symptoms develop that are consistent with liver disease, the risks and benefits of continued SPORANOX[®] use should be reassessed. (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, 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[®] Capsules should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. SPORANOX[®] Capsules should not be used for other indications 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[®] Capsules, discontinue administration.

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.

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

PRECAUTIONS

General: Hepatic enzyme test values should be monitored in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other

medications. Hepatic enzyme test values should be monitored periodically in all patients receiving continuous treatment for more than 1 month, or at any time a patient develops signs or symptoms suggestive of liver dysfunction.

SPORANOX[®] (itraconazole) Capsules should be administered after a full meal. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism.)

Under fasted conditions, itraconazole absorption was decreased in the presence of decreased gastric acidity. The absorption of itraconazole may be decreased with the concomitant administration of antacids or gastric acid secretion suppressors. Studies conducted under fasted conditions demonstrated that administration with 8 ounces of a cola beverage resulted in increased absorption of itraconazole in AIDS patients with relative or absolute achlorhydria. This increase relative to the effects of a full meal is unknown. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism.)

Information for Patients:

- The topical effects of mucosal exposure may be different between the SPORANOX[®] Capsules and Oral Solution. Only the Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis. SPORANOX[®] Capsules should not be used interchangeably with SPORANOX[®] Oral Solution.
- Instruct patients to take SPORANOX[®] Capsules with a full meal.
- 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 report any signs and symptoms that may suggest liver dysfunction so that the appropriate laboratory testing can be done. 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.

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
Anticonvulsants	carbamazepine
Antimycobacterials	rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide ²
Benzodiazepines	alprazolam, diazepam, midazolam, ^{2,3} triazolam ²
Calcium Channel Blockers	dihydropyridines, 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	alfentanil, buspirone, methylprednisolone, trimetrexate, warfarin

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
Non-nucleoside Reverse Transcriptase Inhibitors	nevirapine

Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

¹This list is not all-inclusive.

²Contraindicated with SPORANOX[®] based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)

³For 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.)

Concomitant administration of digoxin and SPORANOX[®] has led to increased plasma concentrations of digoxin.

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. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience 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.

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-∞} of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively.

Non-nucleoside 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.

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.

Other:

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

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.

Itraconazole produced no mutagenic effects when assayed in DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T $\frac{1}{2}$ Cl8 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. SPORANOX[®] should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy. SPORANOX[®] should not be administered to women of childbearing potential for the treatment of onychomycosis unless they are using

effective measures to prevent pregnancy and they begin therapy on the second or third day following the onset of menses. Effective contraception should be continued throughout SPORANOX[®] therapy and for 2 months following the end of treatment.

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 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.

HIV-Infected Patients: Because hypochlorhydria has been reported in HIV-infected individuals, the absorption of itraconazole in these patients may be decreased.

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, the risks and benefits of continued SPORANOX[®] use should be reassessed. (See WARNINGS: Hepatic Effects and PRECAUTIONS: Information for Patients.)

Adverse Events in the Treatment of Systemic Fungal Infections

Adverse event data were derived from 602 patients treated for systemic fungal disease in U.S. clinical trials who were immunocompromised or receiving multiple concomitant medications. Treatment was discontinued in 10.5% of patients due to adverse events. The median duration before discontinuation of therapy was 81 days (range: 2 to 776 days). The table lists adverse events reported by at least 1% of patients.

Treatment of Systemic Fungal Infections:

Adverse Events Occurring with an Incidence of Greater than or Equal to 1%

Body System/Adverse Event	Incidence (%) (N=602)
Gastrointestinal	
Nausea	11
Vomiting	5
Diarrhea	3
Abdominal Pain	2
Anorexia	1
Body as a Whole	
Edema	4
Fatigue	3
Fever	3
Malaise	1
Skin and Appendages	
Rash*	9
Pruritus	3
Central/Peripheral Nervous System	
Headache	4
Dizziness	2
Psychiatric	
Libido Decreased	1
Somnolence	1
Cardiovascular	
Hypertension	3
Metabolic/Nutritional	
Hypokalemia	2
Urinary System	
Albuminuria	1
Liver and Biliary System	
Hepatic Function Abnormal	3
Reproductive System, Male	
Impotence	1

*Rash tends to occur more frequently in immunocompromised patients receiving immunosuppressive medications.

Adverse events infrequently reported in all studies included constipation, gastritis, depression, insomnia, tinnitus, menstrual disorder, adrenal insufficiency, gynecomastia, and male breast pain.

Adverse Events Reported in Toenail Onychomycosis Clinical Trials

Patients in these trials were on a continuous dosing regimen of 200 mg once daily for 12 consecutive weeks.

The following adverse events led to temporary or permanent discontinuation of therapy.

Clinical Trials of Onychomycosis of the Toenail: Adverse Events Leading to Temporary or Permanent Discontinuation of Therapy

Adverse Event	Incidence (%) Itraconazole (N=112)
Elevated Liver Enzymes (greater than twice the upper limit of normal)	4
Gastrointestinal Disorders	4
Rash	3
Hypertension	2
Orthostatic Hypotension	1
Headache	1
Malaise	1
Myalgia	1
Vasculitis	1
Vertigo	1

The following adverse events occurred with an incidence of greater than or equal to 1% (N=112): headache: 10%; rhinitis: 9%; upper respiratory tract infection: 8%; sinusitis, injury: 7%; diarrhea, dyspepsia, flatulence, abdominal pain, dizziness, rash: 4%; cystitis, urinary tract infection, liver function abnormality, myalgia, nausea: 3%; appetite increased, constipation, gastritis, gastroenteritis, pharyngitis, asthenia, fever, pain, tremor, herpes zoster, abnormal dreaming: 2%.

Adverse Events Reported in Fingernail Onychomycosis Clinical Trials

Patients in these trials were on a pulse regimen consisting of two 1-week treatment periods of 200 mg twice daily, separated by a 3-week period without drug.

The following adverse events led to temporary or permanent discontinuation of therapy.

**Clinical Trials of Onychomycosis of the Fingernail:
Adverse Events Leading to Temporary or Permanent Discontinuation of
Therapy**

Adverse Event	Incidence (%) Itraconazole (N=37)
Rash/Pruritus	3
Hypertriglyceridemia	3

The following adverse events occurred with an incidence of greater than or equal to 1% (N=37): headache: 8%; pruritus, nausea, rhinitis: 5%; rash, bursitis, anxiety, depression, constipation, abdominal pain, dyspepsia, ulcerative stomatitis, gingivitis, hypertriglyceridemia, sinusitis, fatigue, malaise, pain, injury: 3%.

Post-marketing Experience

In worldwide post-marketing experience with SPORANOX[®] Capsules in treatment of onychomycosis and/or systemic fungal infections, peripheral edema, 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 rarely liver failure. Rare cases of congestive heart failure and pulmonary edema have been reported. Rare cases of alopecia, hypertriglyceridemia, menstrual disorders, and neutropenia, and isolated cases of neuropathy have also been reported, although the causal association with SPORANOX[®] is uncertain. (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.

Limited data exist 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[®] (itraconazole) Capsules, the adverse event profile was similar to that observed at recommended doses.

DOSAGE AND ADMINISTRATION

SPORANOX[®] (itraconazole) Capsules should be taken with a full meal to ensure maximal absorption.

SPORANOX[®] Capsules is a different preparation than SPORANOX[®] Oral Solution and should not be used interchangeably.

Treatment of Blastomycosis and Histoplasmosis: The recommended dose is 200 mg once daily (2 capsules). If there is no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 100-mg increments to a maximum of 400 mg daily. Doses above 200 mg/day should be given in two divided doses.

Treatment of Aspergillosis: A daily dose of 200 to 400 mg is recommended.

Treatment in Life-Threatening Situations: In life-threatening situations, a loading dose should be used whether given as oral capsules or intravenously.

- IV Injection: the recommended intravenous dose is 200 mg b.i.d. for four consecutive doses, followed by 200 mg once daily thereafter. Each intravenous dose should be infused over 1 hour. The safety and efficacy of SPORANOX[®] Injection administered for greater than 14 days is not known. See complete prescribing information for SPORANOX[®] (itraconazole) Injection.
- Capsules: although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose of 200 mg (2 capsules) three times daily (600 mg/day) be given for the first 3 days of treatment.

Treatment should be continued for a minimum of three 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[®] Capsules and SPORANOX[®] Oral Solution should not be used interchangeably. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

Treatment of Onychomycosis: Toenails with or without fingernail involvement: The recommended dose is 200 mg (2 capsules) once daily for 12 consecutive weeks.

Treatment of Onychomycosis: Fingernails only: The recommended dosing regimen is 2 treatment pulses, each consisting of 200 mg (2 capsules) b.i.d. (400 mg/day) for 1 week. The pulses are separated by a 3-week period without SPORANOX[®].

HOW SUPPLIED

SPORANOX[®] (itraconazole) Capsules are available containing 100 mg of itraconazole, with a blue opaque cap and pink transparent body, imprinted with “JANSSEN” and “SPORANOX 100.” The capsules are supplied in unit-dose blister packs of 3 x 10 capsules (NDC 50458-290-01), bottles of 30 capsules (NDC 50458-290-04) and in the PulsePak[®] containing 7 blister packs x 4 capsules each (NDC 50458-290-28).

Store at controlled room temperature 15°-25°C (59°-77°F). Protect from light and moisture.

Keep out of reach of children.

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