PRODUCT MONOGRAPH

PrSPORANOX®

itraconazole capsules

100 mg

Antifungal Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	capsule 100 mg	None. *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

SPORANOX® (itraconazole) capsules are indicated for the treatment of the following systemic fungal infections in normal, predisposed or immunocompromised patients:

1. Invasive and non-invasive pulmonary aspergillosis.
2. Oral and/or esophageal candidiasis.
3. Chronic pulmonary histoplasmosis.
4. Cutaneous and lymphatic sporotrichosis.
5. Paracoccidioidomycosis.
6. Chromomycosis.
7. Blastomycosis.

The type of organism responsible for the infection should be isolated and identified and other relevant laboratory studies (wet mount, histopathology, serology) should be undertaken as appropriate to confirm diagnosis. Therapy may be initiated prior to obtaining these results when clinically warranted; however, once these results become available, antifungal therapy should be adjusted accordingly.

SPORANOX® capsules are also indicated for the treatment of the following topical fungal infections in normal, predisposed or immunocompromised patients:

8. Dermatomycoses due to tinea corporis, tinea cruris, tinea pedis, and pityriasis versicolor, where oral therapy is considered appropriate.
9. Onychomycosis.

Prior to initiating treatment with SPORANOX® capsules, appropriate nail or skin specimens should be obtained for laboratory testing (KOH preparation, fungal culture, or nail biopsy) in order to confirm the diagnosis of onychomycosis or dermatomycoses.

Since elimination of itraconazole from skin and nail tissues is slower than from plasma, optimal clinical and mycological responses are thus reached 2 to 4 weeks after the cessation of treatment for skin infections and 6 to 9 months after the cessation of treatment for nail infections.

Geriatrics (> 65 years of age):
Clinical data on the use of SPORANOX® capsules in elderly patients are limited. It is advised to use SPORANOX® capsules in these patients only if it is determined that the potential benefit outweighs the potential risks (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Pediatrics (< 18 years of age):
The efficacy and safety of SPORANOX® capsules have not been established in pediatric patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics)**.

CONTRAINDICATIONS

- SPORANOX® capsules should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see **Table 1**, Calcium Channel Blockers; **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions** and **Cardiovascular**, Use in Patients with Underlying Cardiac Disease and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

- Coadministration with SPORANOX® capsules, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, causes increased plasma concentrations of drugs metabolized by this pathway which may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Drugs that are contraindicated in combination with itraconazole are listed in Table 1 (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions** and **DRUG INTERACTIONS, Serious Drug Interactions** and **Overview**).

Table 1: Drugs that are contraindicated with SPORANOX® capsules

Drug Class	Contraindicated Drugs	Clinical Comments
Analgesics	levacetylmethadol (levomethadyl)‡	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.
	methadone	The potential increase in plasma concentrations of methadone when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation and torsade de pointes.
Antiarrhythmics	disopyramide dofetilide‡	The potential increase in plasma concentrations of these drugs when coadministered with

	dronedarone quinidine	SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.
Antibacterials	telithromycin‡, in subjects with severe renal impairment or severe hepatic impairment	The potential increase in plasma concentrations of telithromycin in subjects with severe renal impairment or severe hepatic impairment when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation and torsade de pointes.
Anticoagulants and Antiplatelet Drugs	ticagrelor	The potential increase in plasma concentrations of ticagrelor when coadministered with SPORANOX® may increase the risk of serious adverse reactions, such as bleeding.
Antihelmintics and Antiprotozoals	halofantrine‡	The potential increase in plasma concentrations of halofantrine when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.
Antihistamines	astemizole‡ mizolastine‡ terfenadine‡	The potential increase in plasma concentrations of astemizole, mizolastine or terfenadine when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine ergometrine (ergonovine) ergotamine methylergometrine (methylergonovine)‡ eletriptan	The potential increase in plasma concentrations of ergot alkaloids when coadministered with SPORANOX® may increase the risk of ergotism, i.e., a risk for vasospasm potentially leading to cerebral ischemia and/or ischemia of the extremities. Coadministration of eletriptan with SPORANOX® can elevate plasma eletriptan concentrations which could result in serious adverse events.
Antineoplastics	irinotecan	The potential increase in plasma concentrations of irinotecan when coadministered with SPORANOX® may increase the risk of potentially fatal adverse events.
Antipsychotics, Anxiolytics and Hypnotics	lurasidone oral midazolam‡ pimozide sertindole‡ triazolam	Coadministration of SPORANOX® and oral midazolam or triazolam may cause several-fold increases in plasma concentrations of these drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. The potential increase in plasma concentrations of pimozide when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation and torsade de pointes. The potential increase in plasma concentrations of sertindole when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.
Calcium Channel Blockers	bepridil‡ felodipine lercanidipine‡ nisoldipine‡	Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole. The potential increase in plasma concentrations of calcium channel blockers when co-administered with SPORANOX® may increase the risk of congestive heart failure.
Cardiovascular Drugs, Miscellaneous	ivabradine‡ ranolazine	The potential increase in plasma concentrations of ranolazine when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation. The potential increase in plasma concentrations of

		ivabradine when co-administered with SPORANOX® may increase the risk of excessive bradycardia.
Diuretics	eplerenone	The potential increase in plasma concentrations of eplerenone when coadministered with SPORANOX® may increase the risk of hyperkalemia and hypotension.
Gastrointestinal Drugs	cisapride‡ domperidone	The potential increase in plasma concentrations of these drugs when coadministered with SPORANOX® may increase the risk of serious cardiovascular events including QTc prolongation.
Lipid Regulating Drugs	lovastatin simvastatin	The potential increase in plasma concentrations of lovastatin and simvastatin when coadministered with SPORANOX® may increase the risk of skeletal muscle toxicity, including rhabdomyolysis.
Urological Drugs	fesoterodine, in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment	The potential increase in plasma concentrations of fesoterodin in subjects with moderate to severe renal impairment or moderate to severe hepatic impairment when coadministered with SPORANOX® may increase the risk of serious adverse reactions, including anticholinergic effects.
	solifenacin, in subjects with severe renal impairment or moderate to severe hepatic impairment.	The potential increase in plasma concentrations of solifenacin in subjects with severe renal impairment or moderate to severe hepatic impairment when coadministered with SPORANOX® may increase the risk of serious adverse reactions, including QT prolongation.
Other	colchicine, in subjects with renal or hepatic impairment.	The potential increase in plasma concentrations of colchicine in subjects with renal or hepatic impairment when coadministered with SPORANOX® may increase the risk of potentially fatal adverse events.

‡ Not marketed in Canada.

- SPORANOX® capsules are contraindicated in patients with a known hypersensitivity to itraconazole or its excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

- There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX® capsules to patients with hypersensitivity to other azoles.

- SPORANOX® capsules should not be administered for the treatment of onychomycosis or dermatomycoses (tinea corporis, tinea cruris, tinea pedis, pityriasis versicolor) to pregnant patients or to women contemplating pregnancy.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Congestive Heart Failure: SPORANOX® (itraconazole) capsules should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections.** 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 **CONTRAINDICATIONS, Table 1,** Calcium Channel Blockers**; WARNINGS AND PRECAUTIONS, Cardiovascular,** Use in Patients with Underlying Cardiac Disease; **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

- **Drug Interactions: Coadministration of a number of CYP3A4 substrates with SPORANOX® capsules is contraindicated.** Coadministration with SPORANOX®, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, causes increased plasma concentrations of drugs metabolized by this pathway which may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Drugs that are contraindicated are listed in Table 1 (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Serious Drug Interactions** and **Overview**).

- **Liver Toxicity:** SPORANOX® capsules have 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. It is advisable to monitor liver function. If clinical signs or symptoms develop that are consistent with liver disease, such as anorexia, nausea, vomiting, jaundice, fatigue, abdominal pain, dark urine, or pale stools, treatment should be discontinued and liver function testing performed. Continued use of SPORANOX® capsules or reinstitution of treatment with SPORANOX® capsules is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **ADVERSE REACTIONS**).

General

SPORANOX® 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. SPORANOX® oral solution is indicated only for the treatment of oral and/or esophageal candidiasis.

Due to its pharmacokinetic properties, SPORANOX® capsules are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

In systemic candidosis, if fluconazole-resistant strains of *Candida* species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence it is recommended to have their

sensitivity tested before the start of itraconazole therapy (see **MICROBIOLOGY, Resistance and Cross-Resistance**).

Carcinogenesis and Mutagenesis
See **TOXICOLOGY, Carcinogenicity** for discussion on animal data.

Cardiovascular
Cardiac Dysrhythmias
Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as cisapride‡, methadone, pimozide, levacetylmethadol (levomethadyl)‡ or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Serious Drug Interactions** and **Drug-Drug Interactions**).

‡ Not marketed in Canada.

Use in Patients with Underlying Cardiac Disease
SPORANOX® has been associated with reports of CHF. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg than among those receiving lower total daily doses. This suggests that the risk of heart failure might increase with the total daily dose of itraconazole.

SPORANOX® capsules should not be administered for the treatment of onychomycosis or dermatomycoses in patients with evidence of ventricular dysfunction such as 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.

The benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g., total daily dose), and the individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, treated with caution, and monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, SPORANOX® capsules should be discontinued (see **DRUG INTERACTIONS** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

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 (n=8) of SPORANOX® for injection, a transient asymptomatic decrease of the left ventricular ejection fraction was observed using gated SPECT imaging; this resolved before the next infusion, 12 hours later.

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 coadministering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of SPORANOX® with felodipine or nisoldipine is contraindicated.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Ear/Nose/Throat

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 **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Antiarrhythmics**). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Gastrointestinal

Use in Patients with Decreased Gastric Acidity

Absorption of itraconazole from SPORANOX® capsules is impaired when gastric acidity is decreased. In patients with reduced gastric acidity, whether from disease (e.g., patients with achlorhydria) or from concomitant medication (e.g., AIDS patients taking drugs that reduce gastric acidity), it is advisable to administer SPORANOX® capsules with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**, **Absorption**).

In patients also receiving acid-neutralizing medicines (e.g., aluminum hydroxide), these should be administered at least 2 hours after the intake of SPORANOX® capsules.

Hepatic/Biliary/Pancreatic

Hepatic Effects

Rare cases of serious hepatotoxicity (including liver failure and death) have been observed with SPORANOX® treatment. 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.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with SPORANOX® capsules 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® capsules.

Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction. Such signs and symptoms include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, abdominal pain, dark urine or pale stools (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions** and **ADVERSE REACTIONS**).

Itraconazole binds extensively to plasma proteins.

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population. It is

recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. In a clinical trial in cirrhotic patients, the mean terminal half-life of itraconazole was increased by 131% and its mean C_{max} decreased by 47%. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolized by CYP3A4 (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

Immune

Use in Acquired Immunodeficiency Syndrome (AIDS) and Neutropenic Patients

Studies with itraconazole in neutropenic and AIDS patients have indicated that itraconazole plasma concentrations are lower than those in healthy subjects (particularly in those patients who are achlorhydric); therefore, monitoring of the itraconazole plasma concentrations and a dose adjustment, if necessary, are recommended. In one study, adequate plasma concentrations of itraconazole (measured by HPLC) for antifungal prophylaxis in neutropenic patients were greater than 250 ng/mL.

Inadequate plasma concentrations were frequently found in patients whose antineoplastic therapy predisposed them to very poor oral absorption and frequent vomiting. In this case, antiemetics can be coadministered and it is particularly important that SPORANOX® capsules be administered with meals.

There has been one report of reduced itraconazole absorption when taken with didanosine. Since the excipients in the didanosine formulation are known to have an acid-neutralizing effect, and since the absorption of itraconazole can be affected by the level of acidity in the stomach, it is recommended that didanosine be administered at least 2 hours after dosing with SPORANOX® capsules.

The results from a study in which 8 HIV-infected individuals were treated with zidovudine, 8 ± 0.4 mg/kg/day with or without SPORANOX® capsules 100 mg b.i.d., showed that the pharmacokinetics of zidovudine were not affected during concomitant administration of SPORANOX® capsules.

In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis or histoplasmosis and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Neurologic

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

Renal

Use in Patients with Renal Insufficiency

Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency**).

In a few patients, hypokalemia has been reported. Consequently, serum potassium should be monitored in patients at risk during high-dose itraconazole therapy.

Itraconazole cannot be removed by hemodialysis.

Effects on Ability to Drive and Use Machines

Adverse reactions such as dizziness, visual disturbances and hearing loss have been reported while taking SPORANOX®. These adverse reactions may impair the ability to drive a vehicle and operate machinery (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

Special Populations

Pregnant Women: SPORANOX® capsules should not be used for the treatment of onychomycosis or dermatomycoses in pregnant patients or in women contemplating pregnancy (see **CONTRAINDICATIONS**). SPORANOX® capsules must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the fetus. Itraconazole has been shown to produce teratogenic effects (major skeletal and secondary soft tissue defects) when administered at high doses (40 mg/kg/day, 5 times MRHD or higher) to pregnant rats. When administered to pregnant mice at high doses (80 mg/kg/day, 10 times MRHD or higher) itraconazole has been shown to produce encephaloceles and/or macroglossia.

SPORANOX® should not be administered to women of child-bearing potential for the treatment of onychomycosis or dermatomycoses unless they are using effective measures to prevent pregnancy and they begin therapy on the second or third day following the onset of menses.

In women of child-bearing potential, an effective form of contraception must be used during therapy. Effective contraception should be continued throughout SPORANOX® therapy and for 2 months following the end of treatment.

There is limited information on the use of itraconazole during pregnancy. During post-marketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations, as well as chromosomal and multiple malformations. A causal relationship with SPORANOX® capsules has not been established.

Nursing Women: Itraconazole is excreted in human milk; therefore, the patient should be advised to discontinue nursing while taking SPORANOX® capsules.

Pediatrics (< 18 years of age): The efficacy and safety of SPORANOX® capsules have not been established in pediatric patients. SPORANOX® capsules should not be used in pediatric patients unless the potential benefit outweighs the potential risks.

No pharmacokinetic data are available in pediatric patients. A small number of patients from age 3 to 16 years have been treated with 100 mg/day of itraconazole for systemic fungal infections and no serious adverse events have been reported. Toxicological studies have shown that itraconazole, when administered to rats, can produce bone toxicity. While no such toxicity has

been reported in adult patients, the long-term effect of itraconazole in children is unknown (see **TOXICOLOGY**).

Geriatrics (> 65 years of age): Clinical data on the use of SPORANOX® capsules in elderly patients are limited. It is advised to use SPORANOX® capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

Cystic Fibrosis

In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady-state dosing of itraconazole oral solution using 2.5 mg/kg bid. Steady state concentrations of > 250 ng/mL were achieved in approximately 50% of subjects greater than 16 years of age, but in none of the patients less than 16 years of age. If a patient does not respond to SPORANOX® capsules, consideration should be given to switching to alternative therapy.

Monitoring and Laboratory Tests

Plasma levels 3 to 4 hours after dosing with itraconazole should be monitored in patients requiring treatment for more than one month, in patients with systemic mycoses who have factors predisposing to poor absorption (such as achlorhydria, renal insufficiency, neutropenia, AIDS) or in those who are taking drugs which may alter itraconazole absorption or metabolism (such as rifampicin and phenytoin).

Due to the presence of an active metabolite, monitoring of plasma levels by bioassay will indicate plasma levels roughly 3 times higher than will monitoring by high-performance liquid chromatography, unless solvent conditions for the HPLC assay are adjusted to allow simultaneous detection of both the parent drug and this metabolite (hydroxy-itraconazole).

Liver function monitoring should be done in patients with pre-existing hepatic abnormalities, or those who have experienced liver toxicity with other medications and should also be considered in all patients receiving treatment with SPORANOX® capsules.

Hypokalemia has been reported in a few patients. Therefore, serum potassium should be monitored in patients at risk during high-dose itraconazole therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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. Before consideration is given to reinstituting therapy, the risks and benefits of SPORANOX® use should be reassessed (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

The most frequently reported adverse experiences in association with the use of SPORANOX® were of gastrointestinal origin, such as dyspepsia, nausea, vomiting, diarrhea, abdominal pain and constipation. Other adverse experiences reported very rarely (< 1/10000) include reversible

increases in hepatic enzymes, hepatitis, menstrual disorder, dizziness and allergic reactions (such as pruritus, rash, urticaria and angioedema), peripheral neuropathy, Stevens-Johnson syndrome, alopecia, hypokalemia, edema, congestive heart failure and pulmonary edema.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse experiences during short-term therapy with SPORANOX® capsules occurred in 7.8% of patients. During long-term therapy in patients, most of whom had underlying pathology and received multiple concomitant treatments, the incidence of adverse experiences was higher (20.6%). The most common adverse experiences (reported by at least 1% of patients) during short-term or long-term therapy with SPORANOX® capsules are presented in Table 2.

Table 2: Most common adverse experiences (≥1%) during long-term therapy with SPORANOX® capsules in comparison with short-term therapy

	Short-term Therapy	Long-term Therapy
Total number of patients	12889	916
Body System*/ Adverse Event	Incidence (%)	
Gastrointestinal*	4.4	9.1
Nausea	1.6	2.9
Dermatological*	0.8	4.5
Rash	<1.0	1.6
Pruritus	<1.0	1.3
Central Nervous System*	2.1	4.3
Headache	1.0	1.1
Respiratory System*	<1.0	3.9
Liver and Biliary System*	0.11	2.7
Miscellaneous*	0.7	5.6
Edema	<1.0	1.0

* Rates represent summary of all types of adverse events recorded for the body system.

For 834 clinical trial patients receiving 2-4 cycles of one-week therapy, the most frequently reported adverse events during the treatment and follow-up period were abdominal pain (1.9%), nausea (1.6%) and headache (1.3%).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse experiences have been reported at an incidence greater than 0.5% and less than 1% during short-term therapy with SPORANOX® capsules:

Central and Peripheral Nervous System: dizziness/faintness; vertigo
Gastrointestinal: dyspepsia/epigastric pain/upset stomach; abdominal pain/discomfort; vomiting; pyrosis; diarrhea; gastritis; flatulence/meteorism; constipation; decreased appetite; other gastric complaints
General: edema; pain; fatigue; fever
Immune: allergic reaction
Psychiatric: sleepiness/somnolence
Skin: pruritus; rash

The following adverse experiences have been reported at an incidence of greater than 0.5% but less than 1% of patients during long-term therapy with SPORANOX® capsules:

Cardiovascular: chest pain; hypertension
Central and Peripheral Nervous System: dizziness
Gastrointestinal: vomiting; dyspepsia/epigastralgia; diarrhea; abdominal pain
General: pain; fatigue; fever
Liver and Biliary System: increase in liver enzymes; abnormal liver function tests; jaundice; hepatitis; cirrhosis; hepatocellular damage; abnormal hepatic function
Metabolic and Nutritional: hypokalemia
Respiratory System: bronchitis/bronchospasm; dyspnea; coughing; rhinitis; sinusitis

Abnormal Hematologic and Clinical Chemistry Findings

An increase in liver enzymes and abnormal liver function tests have been reported infrequently in patients treated with SPORANOX®. In post-marketing experience, high triglyceride levels have been reported very rarely.

Post-Market Adverse Drug Reactions

Worldwide post-marketing experiences with the use of SPORANOX® (across all three SPORANOX® formulations: SPORANOX® capsules, SPORANOX® oral solution and SPORANOX® IV) include reports of the adverse events listed below.

Blood and lymphatic system disorders: granulocytopenia, leukopenia, neutropenia, thrombocytopenia
Immune system disorders: serum sickness, angioneurotic edema, anaphylactic, hypersensitivity, anaphylactoid and allergic reactions
Infections and infestations: upper respiratory tract infection
Metabolism and nutrition disorders: hyperglycemia, hypertriglyceridemia, hypokalemia, hypomagnesemia
Psychiatric disorders: confusional state
Nervous system disorders: peripheral neuropathy, paresthesia, hypoesthesia, headache, dizziness, tremor
Eye disorders: visual disturbances, including vision blurred and diplopia
Ear and labyrinth disorders: tinnitus, transient or permanent hearing loss
Cardiac disorders: cardiac failure, congestive heart failure, left ventricular failure, tachycardia
Vascular disorders: hypotension
Respiratory, thoracic and mediastinal disorders: pulmonary edema, dyspnea, dysphonia

Gastrointestinal disorders: pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhea, constipation, dysgeusia, gastrointestinal disorder
Hepatobiliary disorders: serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes, hepatic failure, hyperbilirubinemia
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus, rash erythematous, hyperhidrosis
Investigations: blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood urea increased, gamma-glutamyltransferase increased, hepatic enzyme increased, urine analysis abnormal
Musculoskeletal and connective tissue disorders: myalgia, arthralgia
Renal and urinary disorders: pollakiuria, urinary incontinence, renal impairment
Reproductive system and breast disorders: menstrual disorders, erectile dysfunction
General disorders and administration site conditions: edema, pyrexia, generalized edema, face edema, chills

DRUG INTERACTIONS

Serious Drug Interactions

SPORANOX® capsules is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. Increased plasma concentrations of these drugs, caused by coadministration with itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. Coadministration of a number of CYP3A4 substrates is contraindicated with SPORANOX® capsules. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Drugs that are contraindicated with SPORANOX® capsules are listed below.

levacetylmethadol (levomethadyl)‡, methadone, disopyramide, dofetilide‡, dronedarone, quinidine, telithromycin‡ (in subjects with severe renal impairment or severe hepatic impairment), ticagrelor, halofantrine‡, astemizole‡, mizolastine‡, terfenadine‡, ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)‡, irinotecan, lurasidone, oral midazolam‡, pimozide, sertindole‡, triazolam, bepridil‡, felodipine, lercanidipine‡, nisoldipine‡, ivabradine‡, ranolazine, eplerenone, cisapride‡, domperidone, lovastatin, simvastatin, fesoterodine (in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment), solifenacin (in subjects with severe renal impairment or moderate to severe hepatic impairment), eletriptan, colchicine (in subjects with renal or hepatic impairment).

See **CONTRAINDICATIONS, Table 1; WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions**.

‡Not marketed in Canada.

Overview

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Similarly, itraconazole may modify the pharmacokinetics of other substances that share this metabolic pathway. Itraconazole is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. When using concomitant medication, it is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust dosages.

Interaction mechanisms and related recommendations are described below. Examples of drugs that may potentially interact with itraconazole in a clinically relevant manner, as based on documented evidence or based on the pharmacokinetic and/or pharmacologic profile of the drug, are presented by drug class in Table 3 and Table 4, with clinical recommendations.

1. **Drugs that may decrease itraconazole plasma concentrations**
   a) Drugs that reduce the gastric acidity (e.g., acid neutralizing medicines such as aluminum hydroxide, or acid secretion suppressors such as H_2-receptor antagonists and proton pump inhibitors) impair the absorption of itraconazole from itraconazole capsules.

   b) Coadministration of itraconazole with potent enzyme inducers of CYP3A4 may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be reduced.

2. **Drugs that may increase itraconazole plasma concentrations**
   Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole.

3. **Drugs that may have their plasma concentrations increased by itraconazole**
   Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of drugs metabolized by CYP3A4 and can inhibit the drug transport by P-glycoprotein, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. CYP3A4-metabolized drugs known to prolong the QT interval may be contraindicated with itraconazole, since the combination may lead to ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors, the decline in plasma concentrations may be even more gradual. This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole. This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

   The interacting drugs are categorized as follows:

   CONTRAINDICATED: Under no circumstances is the drug to be coadministered with itraconazole, and up to 2 weeks after discontinuation of treatment with itraconazole. The interacting drugs categorized as CONTRAINDICATED are listed in Table 1 (see **CONTRAINDICATIONS**).

   NOT RECOMMENDED: It is recommended that the use of the drug be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be

avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. The interacting drugs categorized as NOT RECOMMENDED are listed in Table 3.

USE WITH CAUTION: Careful monitoring is recommended when the drug is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. The interacting drugs categorized as USE WITH CAUTION are listed in Table 4.

Drug-Drug Interactions

Table 3: Selected drugs that are predicted to alter the plasma concentration of itraconazole or have their plasma concentration altered by itraconazole[1] are NOT RECOMMENDED be used with itraconazole

Drug Class/Drug Name	Potential Effect on Concentrations	Clinical Comment
Alpha Blockers		
tamsulosin	tamsulosin ↑	**NOT RECOMMENDED**: It is recommended that the use of tamsulosin be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of tamsulosin is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Analgesics		
fentanyl	fentanyl ↑	**NOT RECOMMENDED:** It is recommended that the use of fentanyl be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antibacterials		
isoniazid rifabutin rifampicin	itraconazole ↓	**NOT RECOMMENDED:** Administration of potent enzyme inducers of CYP3A4 such as rifabutin, rifampicin and isoniazid with itraconazole is not recommended. It is recommended that the use of rifabutin, rifampicin and isoniazid be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as

		deemed necessary. See 1b) above for further information.
	rifabutin ↑	**NOT RECOMMENDED**: It is recommended that the use of rifabutin be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Anticoagulants and Antiplatelet Drugs		
apixaban rivaroxaban	apixaban ↑ rivaroxaban ↑	**NOT RECOMMENDED:** It is recommended that the use of these drugs be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Anticonvulsants		
carbamazepine phenobarbital phenytoin	itraconazole ↓	**NOT RECOMMENDED:** Administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these drugs be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary. See 1b) above for further information.
	carbamazepine ↑	It is recommended that the use of carbamazepine be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of carbamazepine is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antineoplastics		
axitinib dabrafenib dasatinib ibrutinib nilotinib sunitinib trabectedin	axitinib ↑ dabrafenib ↑ dasatinib ↑ ibrutinib ↑ nilotinib ↑ sunitinib ↑	**NOT RECOMMENDED:** It is recommended that the use of these drugs be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the

	trabectedin ↑	interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antivirals		
efavirenz nevirapine	itraconazole ↓	**NOT RECOMMENDED:** It is recommended that the use of these drugs be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary. See 1b) above for further information.
simeprevir	simeprevir ↑	**NOT RECOMMENDED:** It is recommended that the use of simeprevir be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Cardiovascular Drugs, Miscellaneous		
aliskiren sildenafil, for the treatment of pulmonary hypertension	aliskiren ↑ sildenafil ↑	**NOT RECOMMENDED:** It is recommended that the use of these drugs be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Immunosuppressants		
everolimus	everolimus ↑	**NOT RECOMMENDED:** It is recommended that the use of everolimus be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Respiratory Drugs		
salmeterol	salmeterol ↑	**NOT RECOMMENDED:** It is recommended that the use of salmeterol be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the

		interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Urological Drugs		
darifenacin vardenafil	darifenacin↑ vardenafil ↑	**NOT RECOMMENDED:** It is recommended that the use of these drugs be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Other		
colchicine conivaptan tolvaptan	colchicine ↑ conivaptan ↑ tolvaptan ↑	**NOT RECOMMENDED:** It is recommended that the use of these drugs be avoided during and up to 2 weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.

[1]This list is not all-inclusive.
[‡]Not marketed in Canada.

Table 4: Selected drugs that are predicted to alter the plasma concentration of itraconazole or have their plasma concentration altered by itraconazole[1] are to be USED WITH CAUTION with itraconazole

Analgesics		
alfentanil buprenorphine iv and sublingual oxycodone sufentanil	alfentanil ↑ buprenorphine ↑ oxycodone ↑ sufentanil ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Analgesics (NSAIDs)		
meloxicam	meloxicam ↓	**USE WITH CAUTION**: Careful monitoring is recommended when meloxicam is coadministered with itraconazole. Upon coadministration, it is recommended that its effects or side effects be monitored, and its dosage be adapted if necessary.
Antiarrhythmics		
digoxin	digoxin ↑	**USE WITH CAUTION:** Careful monitoring is recommended when digoxin is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or

		symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antibacterials		
telithromycin‡	telithromycin ↑	**USE WITH CAUTION:** Careful monitoring is recommended when telithromycin is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
ciprofloxacin clarithromycin erythromycin	itraconazole ↑	**USE WITH CAUTION**: It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured. See 2 above for further information.
Anticoagulants and Antiplatelet Drugs		
coumarins cilostazol dabigatran	coumarins ↑ cilostazol ↑ dabigatran ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antidiabetics		
repaglinide saxagliptin	repaglinide↑ saxagliptin ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antihelmintics and Antiprotozoals		
praziquantel	praziquantel ↑	**USE WITH CAUTION**: Careful monitoring is recommended when praziquantel is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antihistamines		
bilastine‡ ebastine	bilastine ↑ ebastine ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for

		signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antineoplastics		
bortezomib busulphan docetaxel erlotinib gefitinib imatinib ixabepilone lapatinib ponatanib trimetrexate vinca alkaloids	bortezomib ↑ busulphan ↑ docetaxel ↑ erlotinib ↑ gefitinib ↑ imatinib ↑ ixabepilone ↑ lapatinib ↑ ponatanib ↑ trimetrexate ↑ vinca alkaloids ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antipsychotics, Anxiolytics and Hypnotics		
alprazolam aripiprazole brotizolam buspirone haloperidol midazolam IV perospirone quetiapine ramelteon risperidone	alprazolam ↑ aripiprazole ↑ brotizolam ↑ buspirone ↑ haloperidol ↑ midazolam IV perospirone ↑ quetiapine, ↑ ramelteon ↑ risperidone ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Antivirals		
ritonavir-boosted darunavir ritonavir-boosted fosamprenavir indinavir ritonavir telaprevir	itraconazole ↑ indinavir ↑ ritonavir ↑	**USE WITH CAUTION**: It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured. See 2 above for further information. In addition, upon coadministration with indinavir or ritonavir, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
maraviroc saquinavir	maraviroc ↑ saquinavir ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Beta Blockers		
nadolol	nadolol ↑	**USE WITH CAUTION**: Careful monitoring is

		recommended when nadolol is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Calcium Channel Blockers		
other dihydropyridines, verapamil	other dihydropyridines↑ verapamil ↑	**USE WITH CAUTION**: Careful monitoring is recommended when other dihydropyridines such as verapamil is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Cardiovascular Drugs, Miscellaneous		
bosentan riociguat	bosentan ↑ riociguat ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Drugs That Reduce Gastric Acidity		
all acid neutralizing medicines e.g., aluminum hydroxide, H_2-receptor antagonists, proton pump inhibitors (PPIs)	itraconazole ↓	**USE WITH CAUTION**: • It is recommended that itraconazole be administered with an acidic beverage (such as non-diet cola) upon co-treatment with drugs reducing gastric acidity; • It is recommended that acid neutralizing medicines (e.g., aluminum hydroxide) be administered at least 1 hour before or 2 hours after the intake of SPORANOX® capsules; • Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary. See 1a) above for further information.
Gastrointestinal Drugs		
aprepitant	aprepitant ↑	**USE WITH CAUTION**: Careful monitoring is recommended when aprepitant is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Immunosuppressants		
budesonide ciclesonide cyclosporine dexamethasone fluticasone methylprednisolone	budesonide ↑ ciclesonide ↑ cyclosporine ↑ dexamethasone ↑ fluticasone ↑ methylprednisolone ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be

rapamycin (also known as sirolimus) tacrolimus temsirolimus	rapamycin ↑ tacrolimus ↑ temsirolimus ↑	reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Lipid Regulating Drugs		
atorvastatin	atorvastatin ↑	**USE WITH CAUTION**: Careful monitoring is recommended when atorvastatin is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
SSRIs, Tricyclics and Related Antidepressants		
reboxetine	reboxetine ↑	**USE WITH CAUTION**: Careful monitoring is recommended when reboxetine is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of reboxetine, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Urological Drugs		
fesoterodine imidafenacin oxybutynin sildenafil, for the treatment of erectile dysfunction solifenacin tadalafil tolterodine	fesoterodine ↑ imidafenacin ↑ oxybutynin sildenafil ↑ solifenacin ↑ tadalafil ↑ tolterodine ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.
Other		
alitretinoin (oral formulation) cinacalcet mozavaptan	alitretinoin ↑ cinacalcet ↑ mozavaptan ↑	**USE WITH CAUTION**: Careful monitoring is recommended when these drugs are coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. See 3 above for further information.

[1]This list is not all-inclusive.
[‡]Not marketed in Canada.

Drug-Food Interactions

For optimal absorption, SPORANOX® capsules should be taken immediately after a full meal (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
When SPORANOX® therapy is indicated, the type of organism responsible for the infection should be isolated and identified; however, therapy may be initiated prior to obtaining these results when clinically warranted.

SPORANOX® capsules is a different preparation than SPORANOX® oral solution and should not be used interchangeably.

For maximal absorption, it is essential to administer SPORANOX® capsules immediately after a full meal (see **ACTION AND CLINICAL PHARMACOLOGY**). See **WARNINGS AND PRECAUTIONS** for treatment of patients with decreased gastric acidity.

Concomitant administration of SPORANOX® with certain medications may require a dose adjustment for either SPORANOX® or for the other medication (see **DRUG INTERACTIONS**).

In patients also receiving acid neutralizing medicines (e.g., aluminum hydroxide), these should be administered at least 1 hour before or 2 hours after the intake of SPORANOX® capsules.

Special Populations
Pediatrics (< 18 years of age)
The safety and efficacy of SPORANOX® have not been established in pediatric patients. SPORANOX® capsules should not be used in pediatric patients unless the potential benefit outweighs the potential risks.

Geriatrics (> 65 years of age)
Clinical data on the use of SPORANOX® capsules in elderly patients are limited. It is advised to use SPORANOX® capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

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 **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**; **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

Patients with Renal Impairment
Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered (see **WARNINGS AND PRECAUTIONS**, **Renal**; **ACTION AND CLINICAL**

PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

Recommended Dose and Dosage Adjustment

SPORANOX® capsules should be administered at a dose of 100-400 mg/day. Dosage recommendations vary according to the infection treated.

Oral Candidiasis:

The recommended dose is 100 mg daily for 2 weeks. The dose should be increased to 200 mg/day in patients with AIDS and neutropenic patients.

Esophageal Candidiasis:

The recommended dose is 100 mg daily for 4 weeks. The dose should be increased to 200 mg/day in patients with AIDS and neutropenic patients.

Blastomycosis and Chronic Pulmonary Histoplasmosis

The recommended dose is 200 mg once daily. 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 per day should be given in 2 divided doses.

Treatment 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.

Other Systemic Mycoses

Table 56: Dosing recommendations for other systemic mycoses

Indication	Dose	Median Duration
Aspergillosis		
Pulmonary	200 mg o.d.	3-4 months
Invasive pulmonary	200 mg b.i.d.	3-4 months
Sporotrichosis	100 mg o.d.	3 months
Paracoccidioidomycosis	100 mg o.d.	6 months
Chromomycosis		
due to *Fonsecaea pedrosoi*	200 mg o.d.	6 months
due to *Cladosporium carrioni*	100 mg o.d.	3 months

Dermatomycoses

Standard Dosages:

Tinea corporis/Tinea cruris

The recommended dose is 100 mg once daily for 14 consecutive days.

Tinea pedis

The recommended dose is 100 mg once daily for 28 consecutive days.

Pityriasis versicolor

The recommended dose is 200 mg once daily for 7 consecutive days.

Alternative Dosages:

Shorter dosing schedules have also been found to be effective in the treatment of *tinea corporis/tinea cruris* and *tinea pedis*. The shorter dosages are:

Tinea corporis/tinea cruris: 200 mg o.d. for 7 consecutive days;
Tinea pedis: 200 mg b.i.d. for 7 consecutive days.

Equivalency between standard and alternative dosages was not established. Patients with chronic recalcitrant *tinea pedis* may benefit from the standard dosage of a lower daily dose (100 mg) for a longer period of time (4 weeks).

Onychomycosis
The recommended clinical dose for onychomycosis is:
A one-week treatment course consists of 200 mg twice daily for 7 days. Treatment with 2 one-week courses is recommended for fingernail infections and 3 one-week courses for toenail infections. The one-week courses are always separated by a 3-week drug-free interval. Clinical response will become evident as the nail regrows, following discontinuation of the treatment.

Table 6: Recommended clinical dose for onychomycosis

	Pulse* 1				Pulse* 2				Pulse* 3
Site of onychomycosis	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Toenails with or without fingernail involvement	200 mg b.i.d. for 7 days	itraconazole-free weeks			200 mg b.i.d. for 7 days	itraconazole-free weeks			200 mg b.i.d. for 7 days
Fingernails only	200 mg b.i.d. for 7 days	itraconazole-free weeks			200 mg b.i.d. for 7 days				

*A pulse equals a one-week course of treatment.

Tissue Elimination of itraconazole
Elimination of itraconazole from skin and nail tissues is slower than from plasma. Optimal clinical and mycological responses are reached 2 to 4 weeks after the cessation of treatment for skin infections and 6 to 9 months after the cessation of treatment for nail infections.

Missed Dose
Physicians should use clinical judgment based on the type and severity of the infection.

Administration
SPORANOX® capsules must be swallowed whole.

OVERDOSAGE

There is no experience of overdosage with itraconazole; however, based on animal toxicity data, symptoms of a gastrointestinal or central nervous system nature may be expected to occur.

Although no data are available for SPORANOX®, administration of activated charcoal absorbs almost all commonly ingested drugs, and should be administered as quickly as possible to most patients who ingest potentially toxic amounts. Standard supportive treatment should be applied as necessary.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

It has been reported that itraconazole cannot be removed by hemodialysis. No specific antidote is available.

ACTION AND CLINICAL PHARMACOLOGY

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 and yeast cell membranes. This inhibition leads to deteriorated membranes, disturbed enzyme activities, and an uncoordinated synthesis of chitin, all together contributing to the antifungal activity. The inhibition of ergosterol synthesis has been attributed to interference with the reactions involved in the removal of the 14-α-methyl group of the precursor of ergosterol, lanosterol. Itraconazole has a very low affinity for mammalian P450 enzymes in contrast to fungal P450 enzymes. Itraconazole is fungitoxic to dermatophytes and yeasts.

Pharmacodynamics

In vitro

A 50% inhibition of the cholesterol biosynthesis is obtained in vitro in human lymphocytes with itraconazole at a concentration of 4×10^{-7}M, which is more than 100 times the concentration of itraconazole needed to produce a 50% inhibition of the ergosterol synthesis in *Candida albicans*.

Up to a concentration of 10^{-5}M, itraconazole did not inhibit the cytochrome P450 dependent aromatization of androstenedione to estrogens by human placental microsomes.

In vivo

In male volunteers, basal serum levels of cholesterol remained similar to the control values obtained before itraconazole treatment of 100 mg o.d. for one month.

Long-term administration of itraconazole (up to 400 mg/day for up to a maximum of 2 years) indicated a slight decrease in plasma cholesterol in 67 patients who had a baseline cholesterol plasma level higher than 200 mg/dL. Only 9.5% of patients showed a shift to a somewhat higher plasma cholesterol level. Similar results were observed in 29 patients with baseline cholesterol levels of at least 250 mg/dL and itraconazole therapy (50-400 mg/day) for a minimum of 3 months. Twenty-three patients showed a reduction and 6 patients had an increased cholesterol level. In this study, the overall decrease in cholesterol did not coincide with alterations in the triglyceride levels.

There was no significant effect of itraconazole 100 or 200 mg taken daily for 35 days on the serum levels of 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol in 12 volunteers. In volunteers receiving single or multiple doses of itraconazole for up to 30 days, no effect on serum levels of the following hormones were observed: basal plasma cortisol, testosterone, aldosterone, cortisol response to cosyntropin (ACTH) and plasma prolactin and response of plasma prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to an intravenous luteinizing hormone-releasing hormone (LHRH) challenge.

Plasma progesterone and estradiol levels measured once weekly (before, during and for 2 weeks after a 5-week administration period of itraconazole 200 mg/day) and saliva progesterone

concentrations measured daily during the 5-week administration reflected a totally normal hormonal profile throughout the menstrual cycle.

In healthy female volunteers with normal, regular menstrual cycles, a single 300 mg dose of itraconazole taken during the late follicular phase did not modify the circadian variation in plasma 17β-estradiol levels. The same dose taken during the luteal phase had no effects on 17β-estradiol and progesterone levels.

Male patients with superficial mycoses who received 50 or 100 mg itraconazole for up to 2 months showed no change in levels of testosterone, sex hormone-binding globulin (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and estradiol.

In 15 patients with systemic mycoses receiving 200 to 400 mg/day itraconazole, adrenal function was studied before and after 12.4 ± 5 (7-24) months of treatment. No change in the response of plasma cortisol to ACTH stimulation was observed. Average testosterone values measured in these patients before and after itraconazole were not statistically significantly different. However, one of eight patients treated with itraconazole 600 mg/day for severe or refractory systemic fungal infection, demonstrated a blunted cortisol response after one month of treatment. Reduction of the dose to 400 mg/day was associated with resolution of the symptoms associated with adrenal insufficiency and an improved cortisol response.

The administration of 200 mg itraconazole daily for 5 weeks had no significant influence on the heart rate, blood pressure, ECG-intervals and systolic time intervals in volunteers. This finding was confirmed in cancer patients who received 50 mg itraconazole daily for 48 weeks.

In 6 healthy volunteers, itraconazole 200 mg daily did not seem to have a negative influence on immune functions. After 5 weeks of itraconazole treatment, only values for OKT4 positive lymphocyte showed a significant shift from 42 ± 3.3% to 53 ± 3.3%. This increase, as well as shifts in the other immunological parameters, remained within the normal ranges.

Pharmacokinetics

Absorption: The pharmacokinetics of itraconazole after intravenous administration and its absolute oral bioavailability from an oral solution were studied in a randomized crossover study using 6 healthy male volunteers. The total plasma clearance averaged 381 ± 95 mL/min and the apparent volume of distribution averaged 796 ± 185 L. The observed absolute oral bioavailability of itraconazole was 55%.

The oral bioavailability of itraconazole capsules is maximal when the capsules are given immediately after a full meal (see **DETAILED PHARMACOLOGY, Human Pharmacokinetics**).

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H_2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see **WARNINGS AND PRECAUTIONS**, **Gastrointestinal** and **DRUG INTERACTIONS**). Absorption of itraconazole under fasted conditions in these subjects is increased when SPORANOX® capsules are administered with an acidic beverage (such as a non-diet cola). When SPORANOX® capsules were administered as a single 200-mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H_2-receptor antagonist, itraconazole

absorption was comparable to that observed when SPORANOX® capsules were administered alone (see **DRUG INTERACTIONS**).

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given (see **WARNINGS AND PRECAUTIONS, General**).

Distribution: The plasma protein binding of itraconazole is 99.8% and that of hydroxy-itraconazole is 99.5%.

Concentrations of itraconazole in whole blood are 60% of those in plasma. Uptake in keratinous tissues, especially the skin, is up to 5 times higher than in plasma, and elimination of itraconazole is related to epidermal regeneration. Therefore, therapeutic levels in the skin persist for 2 to 4 weeks after discontinuation of a 4-week treatment. Therapeutic levels of itraconazole in nails persist for 6 to 9 months after cessation of treatment. Itraconazole is also present in sebum and to a lesser extent in sweat. Itraconazole is extensively distributed into tissues which are prone to fungal invasion. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be 2 to 3 times higher than the corresponding plasma concentration and the uptake into keratinous tissues, skin in particular, up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma.

Metabolism: Itraconazole is extensively metabolized by the liver into a large number of metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole, which has antifungal activity comparable to itraconazole in vitro. Antifungal drug levels measured by bioassay were about 3 times those of itraconazole assayed by high-performance liquid chromatography. The main metabolic pathways were oxidative scission of the dioxolane ring, aliphatic oxidation at the 1-methylpropyl substituent, N-dealkylation of this 1-methylpropyl substituent, oxidative degradation of the piperazine ring and triazolone scission.

Excretion: Within one week of an oral solution dose, urinary excretion amounted to 35% of the dose and fecal excretion represented 54% of the dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole accounts for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, fecal excretion of unchanged drug ranges from 3% to 18% of the dose.

Special Populations and Conditions

Pediatrics: No pharmacokinetic data are available in pediatric patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Geriatrics: See **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**.

Hepatic Insufficiency: Itraconazole is predominantly metabolized in the liver. Pharmacokinetic data for patients with hepatic insufficiency is limited to subjects who received a single 100 mg dose of SPORANOX® capsules. A pharmacokinetic study using a single 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%; mean cirrhotic C_{max} 87 ± 18 ng/mL, mean healthy C_{max} 164 ± 34 ng/mL) and a two-fold increase in the elimination half-life (37 ± 7 hrs and 16 ± 5 hrs, respectively) 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 (mean cirrhotic AUC 1449 ± 207 ng.h/mL, mean healthy AUC 1856 ± 388 ng.h/mL). Data are not available in cirrhotic patients during long-term use of itraconazole. 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 medicines metabolized by CYP3A4 (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Renal Insufficiency: Limited data are available on the use of itraconazole in patients with renal insufficiency. Caution should be exercised when the drug is administered in this patient population (see **WARNINGS AND PRECAUTIONS, Renal**). Pharmacokinetic data in renally impaired patients is limited to subjects who received a single 200 mg dose of SPORANOX® capsules. 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; continuous ambulatory peritoneal dialysis: n=5). Mean ± SD pharmacokinetic parameters are summarized below.

Table 7: Mean pharmacokinetic parameters in renally impaired patients receiving a single 200 mg oral dose of itraconazole

Patient Group (n)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-8h} (ng.h/mL)
Uremic (7)	4.0 ± 1.2	213 ± 178	1026 ± 819
Hemodialysis			
Off dialysis (7)	4.7 ± 1.4	140 ± 119	634 ± 507
On dialysis (7)	4.1 ± 0.9	113 ± 83	507 ± 371
CAPD (5)	4.4 ± 2.2	77 ± 29	325 ± 107

Plasma concentration vs. time profiles showed wide inter-subject variation in all three groups. In uremic subjects (mean CrCl 13 mL/min/1.73m^2), mean plasma concentrations and overall exposure, based on AUC_∞, were slightly reduced compared with healthy subject in a previous study (AUC_∞ values of 3454 ± 3132 vs. 4161 ± 1949 ng hr/mL in uremic patients and healthy subjects, respectively). C_{max} and AUC_{0-8h} values were reduced 30-40% in hemodialysis patients on non-dialysis days, compared to uremic patients (see Table 7), and further reduced 10-20% on dialysis days. In CAPD patients, C_{max} and AUC_{0-8h} values were reduced to one-third the values seen in non-dialyzed uremic patients.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole (see **WARNINGS AND PRECAUTIONS, Renal** and **DOSAGE AND ADMINISTRATION,** Patients with Renal Impairment).

STORAGE AND STABILITY

SPORANOX® capsules should be stored at room temperature (15-30°C). They should be protected from light and moisture. Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

SPORANOX® capsules are available as pink and blue capsules containing 100 mg of itraconazole in a pellet formulation. Capsules are imprinted in white with "JANSSEN" on the cap and "SPORANOX" on the body.

100

Composition

Each SPORANOX® capsule contains 100 mg of itraconazole as well as: sugar spheres (NF) (composed of maize starch, purified water, and sucrose), hydroxypropylmethylcellulose, gelatin, polyethylene glycol, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22 and D&C Red No. 28.

Packaging

SPORANOX® capsules are supplied in HDPE bottles of 30 and PULSEPAK® cartons of 7 blister cards containing 4 capsules. The PULSEPAK® is specifically designed for use in the treatment of onychomycosis.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

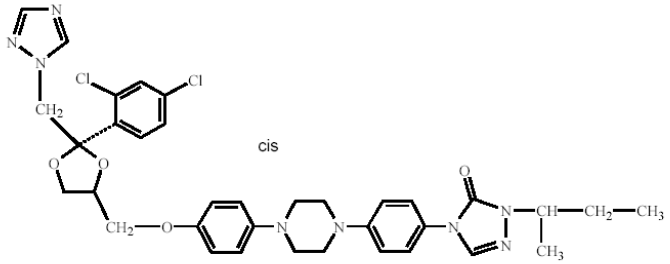
Drug Substance

Proper name: Itraconazole

Chemical name: (±)-cis-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one

Molecular formula and molecular mass: $C_{35}H_{38}Cl_2N_8O_4$, 705.64

Structural formula:



Physicochemical properties: Itraconazole is an almost white to slightly yellow powder, with a pKa of 3.7 and a melting range of 165-169°C. It is highly hydrophobic and lipophilic, with a log partition coefficient of 5.66 in the n-octanol/aqueous buffer solution of pH=8.1.

Itraconazole is very poorly soluble in water (<1 µg/mL) and in diluted acidic solutions (<5 µg/mL).

Concentrations exceeding 1% can only be obtained in some organic solvents such as acidified polyethylene glycols (PEG) or in aqueous cyclodextrin solutions.

DETAILED PHARMACOLOGY

Human Pharmacokinetics

The pharmacokinetics of itraconazole were studied using 6 healthy male volunteers who received, in a cross-over design, single 100 mg doses of itraconazole as a polyethylene glycol capsule, with or without food. The same 6 volunteers also received 50 mg or 200 mg with food in a crossover design. In this study, only itraconazole plasma concentrations were measured.

Table 8: Pharmacokinetic parameters for itraconazole

	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
$AUC_{0-\infty}$ (ng.h/mL)	567 ± 264	1899 ± 838	722 ± 289	5211 ± 2116

Values are means ± standard deviation

Doubling the SPORANOX® dose results in approximately a 3-fold increase in the itraconazole plasma concentrations.

Values given in Table 9 represent data from a crossover pharmacokinetic study in which 27 healthy male volunteers each took a single 200 mg dose of SPORANOX® capsules with or without food.

Table 9: Crossover pharmacokinetic study of itraconazole in healthy male volunteers

	Itraconazole		Hydroxy-itraconazole	
	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
$AUC_{0-\infty}$ (ng.h/mL)	3423 ± 1154	2094 ± 905	7978 ± 2648	5191 ± 2489
$t_{½}$ (hours)	21 ± 5	21 ± 7	12 ± 3	12 ± 3

Values are means ± standard deviation

Steady-state concentrations were reached within 15 days following oral doses of 50-400 mg daily. Values given in Table 10 are data at steady-state from a pharmacokinetic study in which 27 healthy male volunteers took 200 mg SPORANOX® capsules b.i.d. (with food) for 15 days.

Table 10: Steady-state pharmacokinetic study of itraconazole in healthy male volunteers

	Itraconazole	Hydroxy-itraconazole
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
$AUC_{0-\infty}$ (ng.h/mL)	22569 ± 5375	38572 ± 8450
$t_{½}$ (hours)	64 ± 32	56 ± 24

Values are means ± standard deviation

Results of the pharmacokinetic study suggest that itraconazole may undergo saturation metabolism with multiple dosing.

Animal Pharmacodynamics

In general observation tests, the dose of 40 mg/kg, given orally to mice and injected intraperitoneally in rats, was devoid of central actions. In addition, many peripheral (anticholinergic, antidiarrheal, α_1-adrenergic blocking, muscle relaxant, aspirin-like activation) and non-specific actions (hypothermic, toxic) can be excluded from its activity profile.

Itraconazole, at the oral dose of 40 mg/kg in rats was found to be devoid of effects on conditioned food consumption; fecal excretion; urine excretion; castor oil diarrhea; tail withdrawal reaction time; *Mycobacterium butyricum* arthritis (36 mg/kg in the food); and gastric mucosal integrity (40 mg/mL or 100 mg/kg in 0.15 M HCl). Whenever any effects of itraconazole dissolved in PEG 200 were observed, they were identical to those seen with the vehicle alone.

Animal Pharmacokinetics

The absorption, tissue distribution, metabolism and excretion of itraconazole were studied in rats, mice, rabbits and dogs.

Following single oral administration, itraconazole was well absorbed in all species studied. The absolute bioavailability of oral itraconazole in the fasting dog was 48% for the drug given in an aqueous β-cyclodextrin solution and 10-30% for PEG-capsules. After a single oral dose of ^{3}H-itraconazole, the unchanged drug represented on average 20-26% of the plasma radioactivity in rats, 15% in dogs and 10% in man. The terminal plasma half-life of itraconazole was 7 hours in male rats and in rabbits, 16 hours in female rats and about 50 hours in dogs. Hydroxy-itraconazole was the main plasma metabolite in all species studied, and showed an antifungal activity similar to that of itraconazole. The mean AUC ratio of hydroxy-itraconazole to unchanged itraconazole was 1.1 in dogs. The terminal half-life of hydroxy-itraconazole was about 35 hours in dogs.

On repeated administration, steady-state was reached within 2 to 4 days in rats and rabbits and within 2 to 3 weeks in dogs. Average steady-state levels of itraconazole increased proportionally with the dose in rabbits (5 to 80 mg/kg) and dogs (2.5 to 20 mg/kg) and values were consistent with those predicted from single-dose kinetics. In dogs, apparent dose-dependent kinetics were observed for doses higher than 20 mg/kg, due to the limited solubility of the drug in the gastrointestinal fluid. In both dog and man, AUC ratios of hydroxy-itraconazole to itraconazole after repeated administration were similar to those after a single oral dose. In male rats and in male and female mice, there appeared to be a dose-dependent formation of hydroxy-itraconazole, with plasma concentration ratios of hydroxy-itraconazole to itraconazole decreasing from about 3 at 10 mg/kg to 0.5-0.8 at 160 mg/kg.

The plasma protein binding of itraconazole was very high in rats (99.73%) and in dogs (99.79%). The plasma protein binding of hydroxy-itraconazole was very high too, but somewhat lower than that of the parent drug. Nevertheless, the tissue distribution of itraconazole as well as of hydroxy-itraconazole was extensive, as demonstrated by in vivo tissue distribution studies in rats and dogs, and as reflected by the high volume of distribution of itraconazole in dogs (17 L/kg). Highest radioactivity levels were seen in the adrenal gland, in liver, in lacrimatory gland and in fat. Remarkably high concentrations were found in the vaginal fluid and tissue. In most other tissues, including the skin, radioactivity levels were about 2 to 5 times higher than the

corresponding plasma levels. Lowest levels at any time point occurred in the blood and brain. After peak time, tissue levels in female rats were 2 to 4 times higher than in males. Most tissue to plasma concentration ratios of hydroxy-itraconazole were comparable to those of itraconazole in male and female rats, whereas in dog tissues they were about half those of the parent drug. The elimination rate of itraconazole as well as of hydroxy-itraconazole from rat tissues was similar to that from plasma. Placental transfer of itraconazole in the rat was very limited, since only 0.9% of the maternal dose was recovered in the combined fetuses. No undue accumulation occurred either in rats or in dogs after subchronic or chronic administration of itraconazole at very high doses.

The excretion of the radioactivity in rats was very rapid. The predominant excretion in the feces (90%) was related to an extensive biliary excretion (63% in male rats, part of which underwent enterohepatic circulation) and to the excretion of the parent drug (22-29%). In dogs the excretion was slower and amounted to 17% in the urine and 65% in the feces within one week.

Itraconazole was metabolized into more than 30 metabolites in both rats and dogs and in man. The metabolic pathways were very similar in the 3 species. There were some quantitative differences for the mass balance of the metabolites in the 3 species, but all metabolites detected in man were found to some extent also in rats and dogs, both species used in toxicity experiments. Besides hydroxy-itraconazole, which resulted from the (ω-1)-oxidation at the 1-methylpropyl substituent, there were no other antifungally active metabolites.

MICROBIOLOGY

Itraconazole is an orally active triazole antifungal drug which demonstrates antifungal activity on a wide variety of fungi and yeast in vitro. This spectrum includes dermatophytes (e.g., *Microsporum, Trichophyton* and *Epidermophyton* species), yeasts (e.g., *Candida spp*., including *C. albicans, C. tropicalis, C. parapsilosis and C. krusei, Cryptococcus neoformans; Malassezia spp.*), dimorphic fungi (e.g., *Histoplasma spp.* including *H. capsulate; Paracoccidioides brasiliensis, Blastomyces dermatitidis* and *Sporothrix schenckii*), various organisms which cause chromomycosis, and other fungi including *Aspergillus fumigatus*.

MIC_{90}'s for the majority of medically important fungi are between 0.1 and 1.0 µg/mL, while fungicidal activity is obtained at higher concentrations (10 µg/mL). The in vitro activity of hydroxy-itraconazole (the only active metabolite) is comparable to the in vitro activity of itraconazole.

The spectrum of in vitro antifungal activity of itraconazole in brain heart infusion is represented in Table 11.

Table 11: Spectrum of in vitro antifungal activity of itraconazole in brain heart infusion

Fungi	Number tested		Cumulative percentage of strains sensitive at stated concentration (in µg/mL)						
	Species	Strains	0.001	0.01	0.1	1	10	100	>100
Dermatophytes	19	456	3	18.6	94.1	99.3	100		
Candida albicans	1	1401	0.2	8.6	71.0	98.1	99.8	100	
Other *Candida spp*.	17	267	1.9	22.5	87.6	98.1	99.6	100	
Torulopsis spp.	5	245	1.2	10.6	87.3	97.6	99.6	100	
Cryptococcus neoformans	1	33	3	60.6	100	-			
Pityrosporum ovale[1]	1	35	0	0	91.4	100			
Various yeasts	6	55	20	47.3	72.7	92.7	96.4	100	
Aspergillus fumigatus	1	83	0	7.2	68.7	98.8	100		
Various *Aspergillus* & *Penicillium spp*.	19	57	1.8	3.5	63.2	80.1	93.0	100	
Sporothrix schenckii	1	23	0	0	78.3	100			
Dimorphic fungi MP	4	10	30	80	100				
Dimorphic fungi YP	4	10	50	100					
Phaeohyphomycetes	11	27	14.8	29.6	96.3	100			
Eufungi (mycetoma)	10	13	7.7	30.8	76.9	84.6	84.6	92.3	100
Phycomycetes	13	23	4.3	4.3	26.1	73.9	82.6	100	
Various other fungi	27	65	1.5	4.6	33.8	44.6	53.8	75.4	100
Actinomycetales	9	10	0	0	10	10	20	70	100

[1] Test medium: Dixon broth

From: Van Cutsem J, Van Gerven F, Janssen PAJ. The in vitro and in vivo antifungal activity of itraconazole. In: Fromtling RA, ed. Recent trends in the discovery, development and evaluation of antifungal agents. Telesymposia proceedings. Barcelona: J.R. Prous Science Publishers, 1987;182.

In vitro results vary considerably depending on culture medium, inoculum size, conditions of incubation, etc. Because of this variability of in vitro results, most fungi show a higher apparent sensitivity to itraconazole in vivo. The principal fungus types that are not inhibited by itraconazole in vitro are *Zygomycetes* (e.g., *Rhizopus spp*., *Rhizomucor spp*., *Mucor spp.*, and *Absidia spp*.), *Fusarium spp*., *Scedosporium spp*. and *Scopulariopsis spp*.

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

The following in vivo activity of oral itraconazole was observed in experimental animal models of systemic mycoses:

Table 12: In vivo activity oral itraconazole

Infection	Animal	Delay/ duration[a] (days)	% of animals responding at dosage indicated (mg/kg/day)								Response
			1.25	2.5	5	10	20	40	80	160	
Candidiasis	Guinea pig	0/14	27		96						Negative kidney culture
	Rat	0/3		100							Survived 21 days
	Rabbit	+1/7							86[b]		Negative kidney culture
Aspergillosis	Guinea pig	0/14			83	75					Survived 28 days
	Guinea pig	+0/14			50	83					Survived 28 days
	IC[d] guinea pig	0/28			100						Survived 28 days
	IC[d] guinea pig	+1/28			80						Survived 28 days
	Mouse	0/5							47		Negative kidney culture
	Rabbit[c]	+3/14			100						Cured
Cryptococcosis	Guinea pig	+3/35				88	100				Negative culture (CSF excluded)
	Mouse	0/14								53	Negative CSF culture
	Rabbit	+4/14							73[b]		Negative CSF culture
Sporotrichosis	Guinea pig	0/28					80	100			Cured
Histoplasmosis	Guinea pig	0/14				63		100			Cured
Coccidioidomy-cosis	Rat	- 3/14					100[e]				Negative lung culture
	Rat	+7/14					80[e]				Negative lung culture
Paracoccidioid-omycosis	Mouse	0/28				100					Survived 28 days

[a] Delay in start of treatment relative to time of infection/duration of treatment.
[b] 200 mg given to each animal, roughly equivalent to 80 mg/kg/day.
[c] Itraconazole administered intravenously.
[d] IC = immunocompromised by cyclophosphamide, corticosteroids or mechlorethamine.
[e] Actual dosage 16 mg/kg/day.
From: Grant SM, Clissold SP. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs 37;1989:319.

Activity has also been demonstrated in clinical superficial fungal infections caused by *Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Microsporum canis, Malassezia furfur*, and *Epidermophyton floccosum*.

Resistance and Cross-Resistance

A 3-day treatment with itraconazole did not decrease the sensitivity of *C. albicans*, *T. glabrata*, or *C. krusei* to the drug. Similarly, the sensitivity of *M. furfur* was not decreased with a 3-week treatment of itraconazole. Furthermore, after 6 months of itraconazole treatment (200 mg twice weekly), no significant changes in IC_{50} were observed in 250 isolates of *C. albicans* tested. However, the development of resistance and the effects of long-term administration with a wider range of fungal species have not been systematically evaluated.

Cross resistance of strains to azole antifungal agents has been known to occur.

TOXICOLOGY

Acute

The LD_{50} values for itraconazole, 14 days after administration were as follows:

Table 13: LD_{50} values for itraconazole 14 days after administration

ROUTE	SPECIES	NUMBER & SEX OF ANIMALS	LD_{50} IN MG/KG (LIMITS)
Oral	Mouse	60 M & F	>320
	Rat	60 M & F	>320
	Guinea Pig	60 M & F	>160
	Dog (Beagle)	18 M & F	>200
Intravenous	Mouse	80 M & F	46.4 (35.5-60.6)
	Rat	40 M	46.4 (35.5-60.6)
	Rat	40 F	40.0 (30.6-52.3)

Signs of toxicity after oral administration were palpebral ptosis, sedation, hypotonia, tremors, hypothermia, ataxia, diarrhea, loss of righting reflex, piloerection, exophthalmia, convulsions in rodents, and vomiting, licking and slight diarrhea in dogs.

After intravenous administration: similar signs were encountered as with oral administration. In addition, dyspnea was seen in rodents.

In the oral studies in rodents, CNS and GI disturbances and mortality were also present in polyethylene glycol (PEG)-treated animals receiving the maximally tolerated volume (20 mL/kg of body weight). This PEG-related toxicity was not observed in mice or guinea pigs receiving 10 mL/kg body weight, and was less severe in rats receiving 10 mL/kg body weight.

Necropsy revealed no consistent drug-related macroscopic changes.

Long-Term Toxicity

Rats: 3 months

In a 3-month toxicity study, itraconazole was administered orally (gavage) at dose levels of 10, 40, and 160 mg/kg to groups of 20 male and 20 female Wistar rats. Clinical signs of GI disturbances (diarrhea) and deaths (12/40 drug-related, 8 female, 4 male) were observed in rats receiving 160 mg/kg/day. Other changes observed included decreased food consumption and body weight gain; increased serum cholesterol and glucose levels; enlarged adrenals with increased fat accumulation and accumulation of proteinaceous material in macrophages.

In rats receiving 40 mg/kg/day orally, similar but less marked histologic changes were observed, but no drug-related abnormalities were detected in clinical, hematologic, food consumption and body weight parameters. Serum chemistry abnormalities were limited to increased cholesterol levels in rats receiving 10 or 40 mg/kg/day.

Rats: 3 months + 1 month recovery

Itraconazole was administered for 3 months to groups of 20 male and 20 female rats by daily gavage at dose levels of 5, 20 or 80 mg/kg body weight/day. This study included both untreated control rats and control rats which received the vehicle (PEG 400) only. At the end of the dosage period, rats from all groups were sacrificed for pathological examinations. Other rats (groups of 10 males and 10 females) from the untreated control group, the vehicle control group, and the group of rats receiving 80 mg/kg (high dose level) were allowed to live one additional month during which no compound or vehicle was administered (recovery period).

There were no drug-related deaths and no relevant abnormalities in the clinical observations, slit-lamp examinations, food consumption, body weight gain, hematologic parameters or urinalyses. Possible drug-related effects were observed in the serum analyses and post-mortem examinations. All abnormalities were no longer observed one month following the cessation of dosing except for marginally enlarged adrenals and a slight, clearly regressing, increase of the number of foamy cells in the lungs of the 80 mg/kg females.

Beagle dogs: 3 months

Itraconazole was administered orally (gelatin capsules) to groups of 3 male and 3 female dogs for 3 months. The daily dose levels were 2.5, 10 and 40 mg/kg/day. No drug-related changes were observed in the mortality, clinical signs, ophthalmoscopy, food consumption, body weight gain, hematologic parameters, serum chemistry values (except marginally decreased albumin levels in the 10 and 40 mg/kg groups), or urinalyses. Also no drug-related gross lesions were found. In the 40 mg/kg/day group the absolute and relative adrenal weights were increased and the thymus weights were slightly decreased. Histologically, hypertrophy and increased fat, detectable in the adrenals of the dogs receiving 10 mg/kg/day were more pronounced in the dogs receiving 40 mg/kg/day. Marginal lymphatic hypoplasia was detected particularly in the thymuses in the 40 mg/kg/day dogs.

Beagle Dogs: 3 months + 1 month recovery

Itraconazole was also administered daily, via gelatin capsules, for 3 months to groups of 4 female and 4 male dogs at dose levels of 5, 20 or 80 mg/kg body weight/day. This study included both untreated control dogs and control dogs which received the vehicle (PEG 400)

only. At the end of the dosage period, dogs from all groups were sacrificed for pathological examinations. Four other dogs (2 male and 2 female) from the untreated control groups, and the group receiving 80 mg/kg (high dose level) remained under observation for one additional month during which no compound or vehicle was administered (recovery period).

No adverse effects were present in the dogs receiving 5 mg/kg. Body weight gains were marginally and transiently decreased in the 20 mg/kg group. In dogs receiving 80 mg/kg there was progressive weight loss during the entire dosing period. One male in the 80 mg/kg group died and one male of the 80 mg/kg group was sacrificed because of poor health and emaciation. In the dogs receiving 80 mg/kg, food consumption decreased (estimated). Possibly drug-related hematological changes were observed in the 80 mg/kg dogs; serum chemistry examinations revealed nonsignificant trends in the dogs receiving 20 mg/kg and significant changes in the dogs receiving 80 mg/kg. Urinalysis indicated possible drug-related effects in the 80 mg/kg dogs. Other changes observed in the post-mortem examinations of the 80 mg/kg dogs and to a lesser extent, the 20 mg/kg dogs were: swollen adrenals, hypertrophy and vacuolation of the adrenal cortex, foamy macrophages in the lymphoid tissue, and foamy cells in the lungs.

All abnormalities were no longer observed after one month of recovery except for the histologic changes in the adrenals which remained present, but to a much reduced extent in 2 of 4 dogs, and the persistence of much less pronounced, but still somewhat elevated (but within normal limits), haptoglobin and alkaline phosphatase levels. The target organ changes observed in lymphoid tissue, lungs, and liver completely disappeared in the 80 mg/kg recovery group.

Rats: 6 months

Itraconazole was administered to groups of 20 male and 20 female rats admixed in the diet at levels of 10, 40 and 160 mg/100 g food. The dosage levels calculated from the food consumption and body weights were 7, 30 and 160 mg/kg/day for the males and 10, 45 and 357 mg/kg/day for the females. However, there was wastage of the food due to drug-induced overactivity in the male 160 mg/100 g food group and the female 40 and 160 mg/100 g food groups which biased the actual test compound intake calculations.

No adverse effects were found in the eyes. The incidences of drug-related deaths were 1/20 in the males of the 160 mg/100 g food group and 14/20 in the females of the 160 mg/100 g food group. Increased serum cholesterol levels and macroscopic changes indicating increased bone fragility in a few rats were the only observations found in the 10 mg/100 g food group, although a macroscopic bone change was also observed in one control rat. Both of these changes were observed in rats of all dosage levels. The adrenals, kidneys, liver (including clinical pathological parameters), macrophage system (including that of the lung), abdominal mesothelium, ovary, uterus, and bone showed drug-specific histologic changes in the rats receiving 160 mg/100 g food and, to a lesser extent, those receiving 40 mg/100 g food. In general, the females were more severely affected. No drug-related histological changes were observed at 10 mg/100 g food.

Rats: 12 months

Itraconazole was administered to groups of 20 male and 20 female rats via the diet at dosage levels of 5, 20 and 80 mg/100 g food or approximately 5, 20 and 80 mg/kg/day (calculated mean compound intake of 3, 12 and 59 mg/kg/day in the males and 4, 27 and 131 mg/kg/day in the

females). Drug-related overactivity and food wastage were observed in the rats receiving 20 or 80 mg/100 g food. The food consumption was estimated to have been decreased in the males of the 80 mg/100 g food group and the females of the 20 and 80 mg/100 g food groups. The food wastage biased the calculated compound intake in these groups.

No adverse effects were found in the eyes. The incidence of drug-related deaths was 6/20, all of which occurred in the females of the 80 mg/100 g food group. Increased serum cholesterol levels were the only adverse findings present in the rats receiving 5 mg/100 g food. The changes occurring at dose levels of 20 and 80 mg/100 g food were similar to, but less extensive than those found at dose levels of 40 and 160 mg/100 g food in the 6 month study. More specifically, no adverse histologic lesions were found in the male rats receiving 20 mg/100 g food and there were no lesions indicating bone fragility in either the male or the female 5 mg/100 g food groups. In general, the females were more severely affected. No drug-related histological changes were observed at the dose of 5 mg/100 g food.

Dogs: 12 months

Itraconazole was administered, via gelatin capsules, to groups of 4 male and 4 female dogs at dosage levels of 5, 20 or 80 mg/kg/day. One male in the 80 mg/kg/day group that became moribund was sacrificed. All other dogs lived 12 months, but one female receiving 20 mg/kg/day and one female receiving 80 mg/kg/day had a transient period of poor health. No adverse effects were found in the dogs receiving 5 mg/kg/day. The changes in the 20 mg/kg/day group were limited, the most significant being decreased serum calcium, increased serum alanine aminotransferase, and a tendency of the adrenal cortex to hypertrophy. In the dogs receiving 80 mg/kg/day, food consumption and body weight gains were decreased, the serum calcium, total protein, and albumin levels were decreased, and the alkaline phosphatase and alanine aminotransferase levels were increased. When considering the time-dependency, this liver dysfunction was surely not progressing with increasing duration.

At necropsy, the adrenals were enlarged. Histologically, the adrenals showed a tendency toward hypertrophy, the lymph nodes had less copious germinal centres, and in the mesenteric lymph nodes, there was a slightly increased prominence of foamy cells. The thymuses were more involuted; there was increased PAS-positive material in the sinusoidal lining of the liver cells and in the lung there was a tendency toward increased small foci of foamy cells (also noted in the lung of dogs receiving 20 mg/kg/day). No drug-related histological changes were observed at 5 mg/kg/day.

Reproduction and Teratology

Segment I Reproduction Studies

Itraconazole was administered orally by gavage to groups of 24 male and 24 female rats in a segment I study to assess its effects on male and female fertility. The dose levels studied were 10, 40 and 160 mg/kg/day which were administered to males (minimum 60 days prior to mating) and females (14 days prior to mating and a further 8 days during pregnancy). No adverse effects were found in the 10 mg/kg/day groups. There were no effects on fertility in the 40 mg/kg/day groups, but parental toxicity was present. In the 160 mg/kg/day groups, parental toxicity including deaths occurred (2 males, 16 females). In the few surviving females of the 160 mg/kg/day group, pregnancy rates decreased and resorption rates increased, whereas other

fertility parameters such as copulation index, number of corpora lutea, and the number of implantations per pregnant rat were normal. It was concluded that itraconazole had no primary effect on male or female fertility and that any adverse effects on fertility were secondary to the general toxicity seen at a partially lethal level of 160 mg/kg/day. No teratogenic effects were present in this study.

Segment II Reproduction Studies

In rats, itraconazole was administered by gavage (2 studies) and admixed with the diet. The dose levels in all rat studies were 10, 40 and 160 mg/kg/day. In the diet study, where itraconazole was administered to groups of 20 female rats from day 6 through day 15 of pregnancy, maternal toxicity and embryotoxicity were found at 40 and 160 mg/kg/day (100% resorption at 160 mg/kg/day). Teratogenic effects (major skeletal defects or abnormalities secondary to skeletal defects) were present in the offspring of the 40 mg/kg/day females. There were no fetuses of the 160 mg/kg/day dams available. When itraconazole was administered via gavage to groups of 36 females (from day 8 through day 18 of pregnancy) in one study and groups of approximately 20 females (from day 6 through day 15 of pregnancy) in another study, maternal toxicity, embryotoxicity and teratologic changes were observed at 160 mg/kg/day. The only effect noted in the 40 mg/kg/day group was a slightly lowered pup weight in one of the two studies.

In a segment II rabbit study, the dose levels were 5 (17 females), 20 (15 females) and 80 (16 females) mg/kg/day administered by gavage from day 6 through day 18 of pregnancy. Reduced implantation was found in the 20 mg/kg/day dams but this observation is a predosing effect. In this study, no embryotoxicity or teratogenicity was present. A second study was performed with the clinical pellet formulation. Doses administered to groups of 15 female rabbits by gavage were 25, 50 and 100 mg/kg/day from day 6 through day 18 of pregnancy. Slight maternal toxicity was characterized by decreased food consumption during and after dosing of 50 and 100 mg/kg/day. Itraconazole did not produce embryotoxic or teratogenic effects.

Two segment II reproduction studies were also conducted in mice, where itraconazole was administered by gavage from days 6 through 16 of pregnancy. The dose levels were 10, 40 and 160 mg/kg/day in the first study (groups of 24 dosed females) and 40, 80 and 160 mg/kg/day (groups of 30 dosed females) in the second. No adverse effects were found in the dams or fetuses of dams receiving 10 or 40 mg/kg/day. In the 80 and 160 mg/kg/day groups a few malformations (mainly encephaloceles and/or macroglossia) were found. A dose level of 160 mg/kg/day produced both maternal toxicity and embryotoxicity.

In a special segment II teratogenicity study in groups of 10 dosed female rats, it was shown that the embryotoxicity and teratogenicity seen after itraconazole at 160 mg/kg could be reduced by simultaneous administration of arachidonic acid. This protective effect of arachidonic acid is similar to what is known for non-steroidal and steroidal anti-inflammatory drugs. Since itraconazole did not show any relevant in vitro inhibitory activity on the target enzymes of the arachidonic acid pathway, an indirect, adrenal-mediated mechanism was proposed.

To evaluate this hypothesis, adrenalectomy was performed at day 4 of pregnancy in pregnant rats. Adrenalectomy resulted in a reduction of the embryotoxic and teratogenic effects of itraconazole dosed at 40 mg/kg. The data indicate that the adrenal effects seen at high dose levels of itraconazole are, at least partially, responsible for the adverse itraconazole effects on the progeny of pregnant rats.

Segment III Reproduction Studies

Perinatal and postnatal effects were studied in groups of 24 female rats in a segment III study. Itraconazole was administered via gavage at the rates of 5, 20 and 80 mg/kg/day from day 18 of pregnancy through a 3-week lactation period. There were no adverse effects at 5 or 20 mg/kg/day whereas maternal toxicity only was present at the dose level of 80 mg/kg/day. Except for a marginal effect on pup weight at 80 mg/kg, no embryotoxic or teratogenic, or any other adverse effects were noticed in the offspring. In a subsequent, second generation study, no adverse effects on reproduction were noted in rats derived from dams (groups of 10 females) dosed up to 80 mg/kg.

Mutagenicity

Itraconazole was studied for mutagenic potential by the *Salmonella typhimurium* microsomal activation (Ames test), *Drosophila* recessive lethal mutation (*Drosophila melanogaster*), micronucleus formation (male and female rats), dominant lethal mutation (male and female mice), mouse lymphoma L5178Y test system and chromosome aberration (human lymphocytes). No mutagenic potential was demonstrated with any of these tests.

Carcinogenicity

The carcinogenic potential of itraconazole was evaluated in groups of 50 male and female mice and groups of 50 male and female rats with itraconazole administered in the diet for 23 months and 24 months, respectively.

In mice, doses were 5, 20 and 80 mg/kg body weight/day. No toxic effects were observed in any of the exposed males. A temporary body weight decrease and an increased incidence of adrenal pigmentation were observed in females receiving 80 mg/kg body weight/day. Tumour incidences of all dosed groups were comparable to those of the control group.

In rats, the doses were 3.2, 13.4 and 25.5 mg/kg body weight/day for the males and 4.7, 22.5, and 52.4 mg/kg body weight/day for the females. Pathological examination revealed, at the high dose and to a lesser extent at the mid dose, modifications of several organs such as abdominal mesothelia, adrenal, lung, lymph node, mammary gland, female genital tract, pituitary gland, skin with subcutis, thymus and urinary bladder. Male rats treated with the high dose of 25.5 mg/kg body weight/day (3.1x Maximum Recommended Human Dose [MRHD]) had a decrease in body weight gain and slight increase in the incidence of soft tissue sarcoma. These sarcomas may have been a consequence of chronic inflammatory reaction of the connective tissue related to a rat-specific response of hypercholesterolemia which was not observed in dogs or humans. In female rats, there was a slight decrease in body weight gain at the low-dose group and an increased wastage of food at the mid- and high-dose groups. Some altered blood parameters and a slight increase in mortality were observed in the high-dose group. Female rats treated with approximately 50 mg/kg body weight/day (6.25x MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) when compared to the control group. Although the occurrence of squamous cell carcinoma in the lung is extremely rare in untreated rats, the increased incidence in this study was not statistically significant.

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PART III: CONSUMER INFORMATION

PrSPORANOX®
itraconazole capsules

This leaflet is Part III of a three-part "Product Monograph" published when **SPORANOX®** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **SPORANOX®**. Contact your doctor or pharmacist if you have any questions about the drug.

This information is for patients who have been prescribed SPORANOX® capsules for treatment of fungal infections of the skin, mouth, eyes, nails or internal organs. This information does not take the place of discussion between you and your doctor. Only your doctor can decide if SPORANOX® treatment is right for you.

ABOUT THIS MEDICATION

What the medication is used for:
SPORANOX® is a prescription medication used to treat fungal infections of the skin, mouth, eyes, nails or internal organs.

This Consumer Information discusses only the capsule form of SPORANOX®. You will get these capsules in a medicine bottle or a SPORANOX® PULSEPAK®. The PULSEPAK® contains 28 capsules for treatment of your fungal nail infection.

What it does:
SPORANOX® goes into your bloodstream and travels to the site of the infection and kills the fungus causing your disease. Recovery time depends on the disease type and severity.

For fungal nail infections, improved nails may not be obvious for several months after the treatment period is finished because it usually takes about 6 months to grow a new fingernail and 12 months to grow a new toenail. Also, SPORANOX® is present in the nail for a long period of time after treatment has stopped.

With skin infections, the lesions will completely disappear only a few weeks after the end of the treatment. This is typical of fungal patches: the drug kills the fungus itself, but the lesion disappears together with regrowth of healthy skin.

When it should not be used:
- if you have congestive heart failure, SPORANOX® could make it worse. If you have congestive heart failure and you are being treated for a fungal infection of the skin or nails, you should not take SPORANOX®. If you are being treated for another kind of fungal infection and your doctor decides that you need SPORANOX®, be sure to get immediate medical help if you experience signs of heart failure (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**)
- if you are taking certain medications (see **INTERACTIONS WITH THIS MEDICATION**)
- if you have had an allergic reaction to itraconazole or any of the other ingredients in SPORANOX® capsules (see **What the nonmedicinal ingredients are**)
- if you have a fungal infection of the skin or nails and are pregnant or planning to become pregnant

What the medicinal ingredient is:
itraconazole

What the nonmedicinal ingredients are:
The capsules contain sugar spheres (composed of maize starch, purified water and sucrose), hypromellose and macrogol. The capsule itself is composed of titanium dioxide, indigotin, erythrosine and gelatin.

What dosage forms it comes in:
pink and blue capsules, with each capsule containing 100 mg of itraconazole

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Liver toxicity (see **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**)
- Heart problems (see **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**)
- Drug interactions (see **INTERACTIONS WITH THIS MEDICATION**)

SPORANOX® treatment is not for everyone. Your doctor will decide if SPORANOX® is the right treatment for you. Some patients should not take SPORANOX® capsules because they may have certain health problems or may be taking certain medications that could lead to serious or life-threatening medical problems if taken together with SPORANOX®.

Tell your doctor about any other medical conditions you have, or have had, especially heart, lung, liver or kidney conditions.
- If you have a liver problem, your dose of SPORANOX® capsules may have to be adjusted;
- If you have a kidney disorder, your dose of SPORANOX® capsules may have to be adjusted.

Also tell your doctor and pharmacist the name of all the prescription and non-prescription medications you are taking, including dietary supplements and herbal remedies.

BEFORE you use SPORANOX® capsules let your doctor or pharmacist know if:
- you have or have had heart disease, including congestive heart failure;
- you have elevated or abnormal liver enzymes or active liver disease, or have experienced liver toxicity with other drugs;
- you are a neutropenic (low white blood cell count), AIDS, or organ transplant patient. The dose of SPORANOX® capsules may have to be adapted;
- you have cystic fibrosis;
- you have ever had an allergic reaction to itraconazole or any of the other ingredients in SPORANOX® capsules.

SPORANOX® capsules can sometimes cause dizziness, blurred/double vision or hearing loss. If you have these symptoms, do not drive or use machines.

Since scientific information on the use of SPORANOX® capsules in children is limited, it is not recommended for use in children under 18 years of age.

Pregnancy
Do not take SPORANOX® capsules if you are pregnant (unless your doctor knows you are pregnant and decides you need SPORANOX®) or planning to become pregnant within 2 months after you have finished your treatment.

If you are able to become pregnant, do not use SPORANOX® capsules for the treatment of fungal skin or nail infections unless you use effective birth control during SPORANOX® treatment and for 2 months after finishing treatment. Ask your doctor about effective types of birth control.

Breast-feeding
Do not take SPORANOX® capsules if you are breast-feeding or discontinue nursing if you are taking SPORANOX®. SPORANOX® is found in human breast milk.

INTERACTIONS WITH THIS MEDICATION

A wide variety of drugs may interact with SPORANOX® capsules.

Never take SPORANOX® capsules if you are taking any of the following medications:
- terfenadine‡, astemizole‡, mizolastine‡ for allergy;
- bepridil‡, felodipine, nisoldipine, lercanidipine‡, ivabradine‡, ranolazine, eplerenone used to treat angina (crushing chest pain) or high blood pressure;
- ticagrelor used to slow down blood clotting;
- cisapride‡ used to treat certain digestive problems;
- lovastatin and simvastatin which lower cholesterol;
- triazolam and midazolam (oral) ‡ sleeping pills;
- lurasidone, pimozide, sertindole‡ used for psychotic disorders;
- levacetylmethadol (levomethadyl)‡, methadone;
- dihydroergotamine or ergotamine (called ergot alkaloids); used in the treatment of migraine headaches;
- ergometrine (ergonovine) and methylergometrine (methylergonovine)‡ (called ergot alkaloids) used to control bleeding and maintain uterine contraction after child birth;
- eletriptan used to treat migraine headaches;
- halofantrine‡ used to treat malaria;
- irinotecan, an anti-cancer drug;
- disopyramide, dronedarone, quinidine, dofetilide‡ used to treat irregular heart beat rhythms;
- domperidone used to treat nausea and vomiting.

‡ Not marketed in Canada.

If you have kidney or liver impairment, never take SPORANOX® capsules while taking any of the following medications:
- colchicine, a medication to treat gout;
- fesoterodine or solifenacin used to treat overactive bladder;
- telithromycin‡, an antibiotic.

‡ Not marketed in Canada.

Wait at least 2 weeks after stopping SPORANOX® capsules before taking any of these medications.

Medications that can decrease the action of SPORANOX® capsules and are not recommended unless your doctor feels it is necessary:
- carbamazepine, phenytoin, phenobarbital used to treat epilepsy;
- rifampicin, rifabutin, isoniazid used to treat tuberculosis;
- efavirenz, nevirapine used to treat HIV/AIDS.

You should therefore always tell your doctor if you are using any of these products so that the appropriate measures can be taken.

Wait at least 2 weeks after stopping these medications before taking SPORANOX® capsules.

Medications not recommended unless your doctor feels it is necessary:
- axitinib, dabrafenib, dasatinib, ibrutinib, nilotinib, sunitinib, trabectedin; certain medications used in the treatment of cancer;
- aliskiren used to treat hypertension;
- sildenafil, when used to treat pulmonary hypertension (increased blood pressure in the blood vessels in the lungs);
- rifabutin used to treat tuberculosis;
- carbamazepine used to treat epilepsy;
- colchicine used to treat gout;
- conivaptan, tolvaptan used to treat low blood sodium;
- darifenacin used to treat urinary incontinence;
- everolimus, given after an organ transplant;
- fentanyl, a strong medication to treat pain;
- apixaban, rivaroxaban used to slow down blood clotting;
- salmeterol used to improve breathing;
- simeprevir used to treat hepatitis C;
- tamsulosin used to treat male urinary incontinence;
- vardenafil used to treat erectile dysfunction.

Wait at least 2 weeks after stopping these medications before taking SPORANOX® capsules.

Medications that may require a dose change (for either SPORANOX® capsules or the other medication):
- ciprofloxacin, clarithromycin, erythromycin, telithromycin‡, antibiotics;
- bosentan, digoxin, nadolol, riociguat, and certain calcium-channel blockers including verapamil that act on the heart or blood vessels;
- coumarins, cilostazol, dabigatran; that slow down blood clotting;
- methylprednisolone, budesonide, ciclesonide, fluticasone or dexamethasone (medications given by mouth, injection or inhalation for conditions such as inflammations, asthma, and allergies);
- cyclosporine, tacrolimus, temsirolimus or rapamycin (also known as sirolimus), which are usually given after an organ transplant;
- maraviroc, and protease inhibitors: indinavir, ritonavir, ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, saquinavir; used in the treatment of HIV/AIDS;
- telaprevir, used in the treatment of Hepatitis C Virus;
- bortezomib, busulphan, docetaxel, erlotinib, gefitinib, imatinib, ixabepilone, lapatinib, ponatinib, trimetrexate, vinca alkaloids; used in the treatment of cancer;
- buspirone, perospirone, ramelteon, midazolam IV, alprazolam, brotizolam; for anxiety or to help you sleep (tranquillizer);
- alfentanil, buprenorphine, oxycodone, sufentanil; certain strong medications to treat pain;

- repaglinide, saxagliptin used to treat diabetes;
- aripiprazole, haloperidol, quetiapine, risperidone used to treat psychosis;
- aprepitant, certain medications used to treat nausea and vomiting;
- fesoterodine, imidafenacin, oxybutynin, solifenacin, tolterodine; to control irritated urinary bladder;
- sildenafil, tadalafil used to treat erectile dysfunction;
- praziquantel used to treat fluke and tapeworms;
- bilastine‡, ebastine; for allergy;
- reboxetine used to treat depression;
- atorvastatin used to lower cholesterol;
- meloxicam used to treat joint inflammation and pain;
- cinacalcet used to treat an over active parathyroid;
- mozavaptan used to treat low blood sodium;
- alitretinoin (oral formulation) used to treat eczema;
- telithromycin‡ used to treat pneumonia.

‡ Not marketed in Canada.

Always tell your doctor, nurse or pharmacist if you are taking any other medications, either prescription or over-the-counter, herbal medications or natural health products.

PROPER USE OF THIS MEDICATION

Always take SPORANOX® capsules right after a full meal because it is better taken up by the body this way. Swallow the capsules whole with some water.

If you are taking acid-neutralizing medications (i.e., antacids), you should take these at least 1 hour before, or 2 hours after your SPORANOX® capsules. For the same reason, if you take medications that stop the production of stomach acid, you should take your SPORANOX® capsules with a non-diet cola beverage.

Do not use SPORANOX® capsules for a condition for which it was not prescribed. Do not give SPORANOX® capsules to other people, even if they have the same symptoms you have. It may harm them.

Do not switch to SPORANOX® oral solution without talking to your doctor.

The SPORANOX® PULSEPAK®

If you use the PULSEPAK®, you will take SPORANOX® capsules for 1 week and then take no SPORANOX® treatment for the next 3 weeks before repeating the 1-week treatment. This is called "pulse dosing." The SPORANOX® PULSEPAK® contains enough medication for one "pulse" (1 week of treatment). The SPORANOX® PULSEPAK® is used only for fungal nail infections.

The SPORANOX® PULSEPAK® comes with special instructions. It contains 7 blister cards — one for each day of treatment. Each card contains 4 capsules. Looking at the back of the card, fold it back along the dashed line and peel away the backing so that you can remove 2 capsules.

Dosing for Fungal Nail Infection:

- Take 2 capsules in the morning and 2 capsules in the evening. This means you will take 4 capsules a day for 7 days. At the end of 7 days, you will have taken all of the capsules in the PULSEPAK® box.

- After you finish the PULSEPAK®, do not take any SPORANOX® capsules for the next 3 weeks. Even though you are not taking any capsules during this time, SPORANOX® treatment keeps working inside your nails to help fight the fungal infection.

- You will need more than one "pulse" to treat your fungal nail infection. When your doctor prescribes another pulse treatment, be sure to get your refill before the end of week 4.

- Nail lesions take up to 6 to 9 months to disappear after the end of treatment. Once the drug kills the fungus, the nail still needs to grow back, and regrowth takes many months. You should therefore stop treatment as prescribed by your doctor, even though you do not see any improvement.

Usual dose:

Your doctor will decide the right SPORANOX® dose for you, and the length of SPORANOX® treatment, depending on the type of fungus and the place of your infection. You will receive either a bottle of capsules or a PULSEPAK®. Do not skip any doses. Be sure to finish all your SPORANOX® capsules as prescribed by your doctor.

Overdose:

In case of drug overdose, contact a healthcare practitioner (e.g. doctor), hospital emergency department, or regional poison control centre, even if there are no symptoms.

Missed dose:

If you forget to take, or miss, doses of SPORANOX® capsules, ask your doctor what you should do with the missed doses. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects that cause people to stop treatment either for a short time or completely include: skin rash, high triglyceride test results (fats in your blood), high liver test results, and digestive system problems (such as nausea, bloating, and diarrhea).

Other side effects that may occur with SPORANOX® treatment include upset stomach, vomiting, abdominal pain, constipation or excess gas in stomach, cough, fluid in the lungs, altered voice, inflammation of the sinuses, inflammation of the nose, upper respiratory tract infection, headache, dizziness, menstrual disorders, erectile dysfunction, confusion, tremor, sleepiness, fatigue, chills, muscle weakness or pain, painful joints, pain, chest pain, swelling, generalized swelling, unpleasant taste, hair loss, inflammation of the pancreas, fever or excessive sweating may also occur.

Report any side effects to your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect *The following side effects are all uncommon:*	Talk with your doctor or pharmacist immediately		Stop taking drug and call your doctor or pharmacist immediately
	Only if severe	In all cases	
Heart Problems			
• Develop shortness of breath		✓	
• Unusual swelling of feet, ankles or legs		✓	
• Sudden weight gain		✓	
• Unusually tired		✓	
• Cough up white or pink phlegm		✓	
• Unusual fast heartbeats		✓	
• Begin to wake up at night		✓	
Liver Problems			
• Unusually tired			✓
• Loss of appetite			✓
• Nausea			✓
• Abdominal pain			✓
• Vomiting			✓
• Yellow colour to skin or eyes			✓
• Dark-coloured urine			✓
• Pale stools			✓
Nerve Problems			
• Tingling			✓
• Numbness			✓
• Reduced sense of touch			✓
• Weakness in the limbs			✓
• Pain			✓
• Pins and needles			✓
• Prickling or burning			✓
Hypersensitivity			
• Skin rash			✓
• Itching			✓
• Hives			✓
• Difficulty breathing or shortness of breath and/or swelling of the face			✓
Severe Skin Disorder			
• Widespread rash with peeling skin and blisters in the mouth, eyes and genitals or			✓
• Rash with small pustules or blisters			✓
Other			
• Blurry or double vision		✓	
• Ringing in ears		✓	
• Oversensitivity to sunlight			✓
• Loss of ability to control urine or urinate much more than usual		✓	
• Hearing loss symptoms[a]			✓

[a] Cases of temporary or permanent hearing loss have been reported in patients taking SPORANOX®

This is not a complete list of side effects. For any unexpected effects while taking SPORANOX® capsules, contact your doctor or pharmacist.

HOW TO STORE IT

Keep all medications, including SPORANOX® capsules, out of the reach and sight of children.

Store SPORANOX® capsules and the PULSEPAK® at room temperature (15°C-30°C) in a dry place protected from light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http:// www.janssen.ca
or by contacting the sponsor, Janssen Inc., at 1-800-567-3331 or 1-800-387-8781.

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