

PRODUCT MONOGRAPH

Pr SPORANOX^{®*}

itraconazole

oral solution 10 mg/mL

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	Solution 10 mg/mL	None. <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

SPORANOX[®] (itraconazole) oral solution 10 mg/mL is indicated for the treatment of oral and/or esophageal candidiasis in adult HIV-positive or other immunocompromised patients.

SPORANOX[®] oral solution as treatment for oral and/or esophageal candidiasis was not investigated in neutropenic patients. Due to the pharmacokinetic properties (see **Product Monograph Part II: DETAILED PHARMACOLOGY, Human Pharmacokinetics**), SPORANOX[®] oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis.

Note: SPORANOX[®] oral solution and SPORANOX[®] capsules should not be used interchangeably.

Geriatrics (> 65 years of age):

The efficacy and safety of SPORANOX[®] oral solution have not been established in geriatric patients (see **WARNINGS AND PRECAUTIONS, Geriatrics**).

Pediatrics (< 18 years of age):

The efficacy and safety of SPORANOX[®] oral solution have not been established in pediatric patients (see **WARNINGS AND PRECAUTIONS, Pediatrics**).

CONTRAINDICATIONS

- **Congestive Heart Failure**
SPORANOX[®] oral solution should not be administered to patients with evidence of ventricular dysfunction, such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see **WARNINGS AND PRECAUTIONS – Serious Warnings and Precautions** and **Cardiovascular, Use in Patients with Underlying Cardiovascular Disease, ADVERSE REACTIONS - Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS - Drug-Drug Interactions, Calcium Channel Blockers**).
- **Drug Interactions**
Coadministration of the following drugs is contraindicated with SPORANOX[®] oral solution (see **WARNINGS AND PRECAUTIONS – Serious Warnings and Precautions** and **DRUG INTERACTIONS – Serious Drug Interactions**):
 - CYP3A4 metabolized substrates that can prolong the QT-interval e.g., cisapride, dofetilide, levacetylmethadol (levomethadyl), pimozide, and quinidine are contraindicated with SPORANOX[®] oral solution. Co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and serious cardiac arrhythmias
 - CYP3A4 metabolized HMG-CoA reductase inhibitors such as lovastatin and simvastatin
 - Triazolam and oral midazolam
 - Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)
 - Eletriptan
 - Nisoldipine
- SPORANOX[®] oral solution is 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 no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX[®] oral solution to patients with hypersensitivity to other azoles.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Congestive Heart Failure:** SPORANOX[®] oral solution should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections. If signs or symptoms of congestive heart failure occur during administration of SPORANOX[®] oral solution, discontinue administration. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS - Cardiovascular, Use in Patients with Underlying Cardiac Disease, ADVERSE REACTIONS - Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS - Drug-Drug Interactions, Calcium Channel Blockers**).
- **Drug Interactions:** Coadministration of cisapride, pimozide, quinidine, dofetilide or levacetylmethadol (levomethadyl) with SPORANOX[®] (itraconazole) capsules or oral solution is contraindicated. SPORANOX[®], a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine concomitantly with SPORANOX[®] and/or other CYP3A4 inhibitors (see **CONTRAINDICATIONS and DRUG INTERACTIONS - Serious Drug Interactions; Overview and Drug-Drug Interactions**).
- **Liver Toxicity:** SPORANOX[®] oral solution has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment. 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[®] oral solution or reinstatement of treatment with SPORANOX[®] oral solution is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk (see **WARNINGS AND PRECAUTIONS - General; Hepatic/Biliary/Pancreatic, Hepatic Effects/Use in Patients with Hepatic Impairment and ADVERSE REACTIONS**).

General

SPORANOX[®] oral solution and SPORANOX[®] capsules should not be used interchangeably. SPORANOX[®] oral solution is indicated only for the treatment of oropharyngeal and/or esophageal candidiasis. The efficacy of SPORANOX[®] oral solution for other indications is unknown. The two dosage forms have different absorption profiles (see ***Product Monograph Part II: DETAILED PHARMACOLOGY - Human Pharmacokinetics***). SPORANOX[®] oral solution contains the excipient hydroxypropyl- β -cyclodextrin, which produced adenocarcinomas of the exocrine pancreas in a rat but not in a similar mouse carcinogenicity study (see ***Product Monograph Part II: TOXICOLOGY - Carcinogenicity***). The clinical relevance of these findings is unknown.

Patients on Continuous Treatment

In patients receiving continuous treatment of more than one month and in patients developing symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine, it is advisable to monitor liver function. If tests are abnormal, treatment should be terminated.

Carcinogenesis and Mutagenesis

See ***Product Monograph Part II: TOXICOLOGY - Carcinogenicity*** for discussion on animal data.

Cardiovascular

Cardiac Dysrhythmias

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, 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**).

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[®] oral solution should not be used in patients with evidence of ventricular dysfunction such as CHF or a history of CHF 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; and 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, itraconazole should be discontinued (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

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[®] and nisoldipine is contraindicated.

Cases of congestive heart failure (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**). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Hepatic/Biliary/Pancreatic

Hepatic Effects/Use in Patients with Hepatic Impairment

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[®] oral solution 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[®] oral solution. 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** box; **General**, and **ADVERSE REACTIONS - Post-Market Adverse Drug Reactions**).

Itraconazole binds extensively to plasma proteins.

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. In cirrhotic patients, the mean terminal half-life of itraconazole was increased by 131% and its mean C_{max} decreased by 47% (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**). Caution should be exercised when this drug is administered in this patient population.

Neurologic

If neuropathy occurs that may be attributable to SPORANOX[®] oral solution, 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. Caution should be exercised when this drug is administered in this patient population (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 dialysis.

Special Populations

Women of Child-Bearing Age: 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.

Pregnant Women: There are no studies available on the use of itraconazole in pregnant women. SPORANOX[®] oral solution should only be given to pregnant women in life-threatening cases and when in these cases the potential benefit 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 the maximum recommended human dose (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.

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[®] oral solution has not been established.

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

Pediatrics (< 18 years of age):

The efficacy and safety of SPORANOX[®] oral solution have not been established in pediatric patients. A pharmacokinetic study was conducted with SPORANOX[®] oral solution in 26 pediatric patients, ages 6 months to 12 years, requiring systemic antifungal treatment. Itraconazole was dosed at 5 mg/kg once daily for 2 weeks and no serious unexpected adverse events were reported (see **Product Monograph Part II: DETAILED PHARMACOLOGY - Human Pharmacokinetics**).

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 *Product Monograph Part II: TOXICOLOGY*).

Since clinical data on the use of SPORANOX[®] oral solution in pediatric patients is limited, SPORANOX[®] oral solution should not be used in children unless the potential benefit outweighs the potential risks.

Geriatrics (> 65 years of age): Since clinical data on the use of SPORANOX[®] oral solution in elderly patients is limited, it is advised to use SPORANOX[®] oral solution in these patients only if the potential benefit outweighs the potential risks.

Cystic Fibrosis:

In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady-state dosing of oral solution using 2.5 mg/kg b.i.d. 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[®] oral solution, consideration should be given to switching to alternative therapy.

Use in Acquired Immunodeficiency Syndrome (AIDS) and Neutropenic Patients:

Studies with SPORANOX[®] capsules 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). However, the bioavailability of itraconazole oral solution, when tested in AIDS patients, was found satisfactory and not altered by the stage of HIV infection.

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.

Monitoring and Laboratory Tests

Due to the presence of an active metabolite, hydroxy-itraconazole, plasma levels monitored by bioassay will yield plasma levels roughly three times higher than that obtained by high-pressure liquid chromatography (HPLC), unless solvent conditions for the HPLC assay are adjusted to allow simultaneous detection of both the parent drug and the metabolite.

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[®] oral solution.

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 reinstating therapy, the risks and benefits of SPORANOX[®] use should be reassessed (see **WARNINGS AND PRECAUTIONS, General** and **Hepatic/Biliary/Pancreatic**).

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.

SPORANOX[®] Oral Solution

The adverse event profile was analyzed for 889 HIV-positive and other immunocompromised patients receiving SPORANOX[®] oral solution for the treatment of oral and esophageal candidiasis. The most frequently reported adverse events were of gastrointestinal origin. The total observed incidence of adverse events that are possibly or directly drug related, during treatment or within 14 days post-treatment for itraconazole oral solution is 18.2%. A listing of adverse events reported with a frequency $\geq 1\%$ for itraconazole in all worldwide studies of oropharyngeal and esophageal candidiasis is presented in Table 1.1.

Table 1.1 - Adverse experience incidence $\geq 1.0\%$ in worldwide trials of oropharyngeal and esophageal candidiasis, by body system

Body System/adverse event	itraconazole n=889
Gastrointestinal system disorder	12.3%
Nausea	5.3%
Diarrhea	4.5%
Vomiting	3.4%
Abdominal pain	2.5%
Skin and appendages disorders	2.4%
Rash	1.3%
Central and peripheral nervous system	1.7%
Headache	1.1%
Liver and biliary system disorders	1.3%
Special senses	1.1%
Taste perversion	1.0%
Body as a whole	1.0%

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 the adverse events listed below.

Blood and lymphatic system disorders: leukopenia, neutropenia, thrombocytopenia
Immune system disorders: serum sickness, angioneurotic edema, anaphylactic, anaphylactoid and allergic reactions
Metabolism and nutrition disorders: hypertriglyceridemia, hypokalemia
Nervous system disorders: peripheral neuropathy, paresthesia, hypoesthesia, headache, dizziness
Eye disorders: visual disturbances, including vision blurred and diplopia
Ear and labyrinth disorders: tinnitus, transient or permanent hearing loss
Cardiac disorders: congestive heart failure
Respiratory, thoracic and mediastinal disorders: pulmonary edema, dyspnea
Gastrointestinal disorders: pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhea, constipation, dysgeusia
Hepatobiliary disorders: serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus
Musculoskeletal and connective tissue disorders: myalgia, arthralgia
Renal and urinary disorders: pollakiuria, urinary incontinence
Reproductive system and breast disorders: menstrual disorders, erectile dysfunction
General disorders and administration site conditions: edema, pyrexia

DRUG INTERACTIONS

Serious Drug Interactions

- Concomitant administration of SPORANOX[®] oral solution with levacetylmethadol (levomethadyl), dofetilide, quinidine, cisapride and pimozone may result in serious cardiovascular events.
- Concomitant administration of SPORANOX[®] oral solution with ergot alkaloids, such as dihydroergotamine, ergometrine, ergotamine and methylergometrine (methylergonovine) may result in serious and/or life-threatening ischemia.
- Concomitant administration of SPORANOX[®] oral solution with HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, may increase the risk of skeletal muscle toxicity including rhabdomyolysis.
- Concomitant administration of SPORANOX[®] oral solution with benzodiazepines, such as midazolam and triazolam, could potentiate and prolong hypnotic and sedative effects.
- Concomitant administration of SPORANOX[®] with fentanyl could increase or prolong fentanyl plasma concentrations and may cause potentially fatal respiratory depression.
- Concomitant administration of eletriptan with SPORANOX[®] can elevate plasma eletriptan concentrations which could result in serious adverse events.
- Concomitant administration of SPORANOX[®] and nisoldipine is contraindicated.

(See **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS**, and

Drug-Drug Interactions.)

Overview

Itraconazole and its major metabolite, hydroxy-itraconazole, are inhibitors of CYP3A4. Therefore, the following drug interactions may occur (see Table 1.2 below and the drug class subheadings that follow):

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

Drug-Drug Interactions

Table 1.2 - Selected drugs that are predicted to alter the plasma concentration of itraconazole or have their plasma concentration altered by itraconazole¹

Drug plasma concentration increased by itraconazole	
Antiarrhythmics	digoxin, dofetilide ² , quinidine ² , disopyramide
Anticonvulsants	Carbamazepine
Antimycobacterials	Rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide ²
Benzodiazepines	alprazolam, diazepam, midazolam ^{2,3} , triazolam ²
Calcium Channel Blockers	dihydropyridines (including nisoldipine ²), verapamil
Ergot Alkaloids	dihydroergotamine ² , ergometrine (ergonovine) ² , ergotamine ² , methylergometrine (methylergonovine) ²
Gastrointestinal Motility Agents	cisapride ²
Glucocorticosteroids	budesonide, dexamethasone, methylprednisolone, fluticasone
HMG-CoA Reductase Inhibitors	atorvastatin, cerivastatin, lovastatin ² , simvastatin ²
5-HT ₁ Receptor Agonists	eletriptan ²
Immunosuppressants	cyclosporine, tacrolimus, sirolimus
Oral Hypoglycemics	oral hypoglycemics (i.e., repaglinide)
Protease Inhibitors	indinavir, ritonavir, saquinavir
Oral Anticoagulants	Warfarin
Other	alfentanil, buspirone, trazodone, trimetrexate, fentanyl, levacetylmethadol (levomethadyl) ² , halofantrine, cilostazol
Decrease plasma concentration of itraconazole	
Anticonvulsants	carbamazepine, phenobarbital, phenytoin
Antimycobacterials	isoniazid, rifabutin, rifampin
Gastric Acid Suppressors/Neutralizers	antacids, H ₂ -receptor antagonists, proton pump inhibitors
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine
Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, lopinavir/ritonavir, ritonavir

¹This list is not all-inclusive.

²Contraindicated with SPORANOX[®] based on clinical and/or pharmacokinetic studies (see **WARNINGS AND PRECAUTIONS** and below).

³For information on parenterally administered midazolam, see the benzodiazepine paragraph below.

Antiarrhythmics: The class IA antiarrhythmics quinidine and disopyramide and class III antiarrhythmics, such as dofetilide, are known to prolong the QT interval. Coadministration of quinidine or dofetilide with SPORANOX[®] may increase plasma concentrations of quinidine or dofetilide which could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] and quinidine or dofetilide is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Concomitant administration of digoxin or disopyramide and SPORANOX[®] has led to clinically significant increases in plasma concentrations of digoxin (likely via inhibition of P-glycoprotein) or disopyramide. Patients should be carefully monitored if SPORANOX[®] is coadministered with either of these drugs.

Anticonvulsants: Reduced plasma concentrations of itraconazole were reported when SPORANOX[®] was administered concomitantly with phenytoin. Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of SPORANOX[®] and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, in vivo studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX[®] and carbamazepine may inhibit the metabolism of carbamazepine.

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

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

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

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

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

Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (e.g., nifedipine and felodipine) and verapamil. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of SPORANOX[®] and nisoldipine is contraindicated. (See **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions** for more information).

Ergot Alkaloids: Concomitant administration of SPORANOX[®] with ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) is contraindicated due to the risk of cerebral and/or peripheral ischemia (see **CONTRAINDICATIONS**). In some cases, concomitant use of potent CYP3A4 inhibitors (protease inhibitors, macrolide antibiotics and antifungal agents) with ergot alkaloids has resulted in serious and/or life-threatening ischemia, including fatalities and cases of gangrene.

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

Gastrointestinal Motility Agents: Coadministration of SPORANOX[®] with cisapride can elevate plasma cisapride concentrations which could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] with cisapride is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Glucocorticosteroids: SPORANOX[®] markedly increased systemic exposure to oral and intravenous dexamethasone (3.7-fold and 3.3-fold increases, respectively), inhaled budesonide (4.2-fold increase), fluticasone and methylprednisolone, and enhanced their adrenal-suppressant effect. Careful follow-up is recommended when itraconazole is coadministered with these drugs.

HMG-CoA Reductase Inhibitors: Human pharmacokinetic data suggest that SPORANOX[®] inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of SPORANOX[®] with HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

5-HT₁ Receptor Agonists: Coadministration of eletriptan with SPORANOX[®] can elevate plasma eletriptan concentrations which could result in serious adverse events. Therefore, concomitant use of eletriptan with SPORANOX[®] is contraindicated (see **CONTRAINDICATIONS**).

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

Macrolide Antibiotics: Erythromycin and clarithromycin are known inhibitors of CYP3A4 (see Table 1.2) and may increase plasma concentrations of itraconazole. In a small pharmacokinetic study involving HIV-infected patients, clarithromycin was shown to increase plasma concentrations of itraconazole. Similarly, following administration of 1 gram of erythromycin

ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and $AUC_{0-\infty}$ of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively.

Non-nucleoside Reverse Transcriptase Inhibitors: Nevirapine is an inducer of CYP3A4. In vivo studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX[®] and nevirapine is not recommended.

Nucleoside Reverse Transcriptase Inhibitors: In a clinical study, when 8 HIV-infected subjects were treated concomitantly with SPORANOX[®] capsules 100 mg twice daily and the nucleoside reverse transcriptase inhibitor zidovudine 8 ± 0.4 mg/kg/day, the pharmacokinetics of zidovudine were not affected. Other nucleoside reverse transcriptase inhibitors have not been studied.

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

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

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

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

Other:

- Levacetylmethadol (levomethadyl) is known to prolong the QT interval and is metabolized by CYP3A4. Co-administration of levacetylmethadol with SPORANOX[®] could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] and levacetylmethadol is contraindicated.
- Halofantrine has the potential to prolong the QT interval at high plasma concentrations. Caution is advised when SPORANOX[®] and halofantrine are administered concomitantly.
- In vitro data suggest that alfentanil is metabolized by CYP3A4. Administration with SPORANOX[®] may increase plasma concentrations of alfentanil.
- Human pharmacokinetic data suggest that concomitant administration of SPORANOX[®] and buspirone results in significant increases in plasma concentrations of buspirone.
- Itraconazole may lead to substantial increases in trazodone plasma concentrations with the potential for adverse effects. A lower dose of trazodone should be considered.

- In vitro data suggest that trimetrexate is extensively metabolized by CYP3A4. An in vitro rat liver model demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX[®] and trimetrexate may inhibit the metabolism of trimetrexate.
- Cilostazol is a CYP 3A4 metabolized drug that should be used with caution when co-administered with SPORANOX[®].
- Fentanyl plasma concentrations could be increased or prolonged by concomitant use of SPORANOX[®] and may cause potentially fatal respiratory depression.

Drug-Food Interactions

For optimal absorption, SPORANOX[®] oral solution should be taken without food (see *Product Monograph Part II: DETAILED PHARMACOLOGY - Human Pharmacokinetics, Absorption*).

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[®] oral solution may be 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.

For optimal absorption, itraconazole oral solution should be taken without food.

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, Hepatic Effects/Use in Patients with Hepatic Impairment; 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. Caution should be exercised when this drug is administered in this patient population (see **WARNINGS AND PRECAUTIONS, Renal, Use in Patients with Renal Insufficiency; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

Recommended Dose and Dosage Adjustment

Oral Candidiasis: The recommended dosage of itraconazole oral solution for oral candidiasis is 200 mg daily in a single dose or divided doses; treatment should continue for 1-2 weeks to decrease the likelihood of relapse.

Esophageal Candidiasis: The recommended dosage for esophageal candidiasis is 100 mg daily for a minimum treatment of three weeks. Treatment should continue for two weeks following resolution of symptoms. Doses of up to 200 mg per day may be used based on medical assessment of the patient's response to therapy.

Administration

The solution should be swished in the oral cavity and swallowed. There should be no rinsing after swallowing.

OVERDOSAGE

There is no experience of overdosage with SPORANOX[®] oral solution; 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.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre
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ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Itraconazole, a triazole derivative, has a broad-spectrum activity; with respect to *Candida* spp., its activity includes *C. albicans*, *C. glabrata* and *C. krusei*.

In vitro studies have demonstrated that itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is a vital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.

Pharmacodynamics

See ***Product Monograph Part II: DETAILED PHARMACOLOGY.***

Pharmacokinetics

Absorption: The oral bioavailability of itraconazole is maximal when SPORANOX[®] oral solution is taken without food. During chronic administration, steady-state is reached after 1-2 weeks. Peak plasma levels are observed 2 hours (fasting) to 5 hours (with food) following oral administration. After repeated once-a-day administration of itraconazole 200 mg in fasting condition, steady-state plasma concentrations of itraconazole fluctuate between 1 and 2 µg/mL

(trough to peak). When the oral solution is taken with food, steady-state plasma concentrations of itraconazole are about 25% lower.

Distribution: The plasma protein binding of itraconazole is 99.8%. Itraconazole is extensively distributed into tissues that are prone to fungal invasion. Concentrations in human lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than the corresponding plasma concentration.

Metabolism: Itraconazole is extensively metabolized by the liver into a large number of metabolites. One of the metabolites is hydroxy-itraconazole, which has in vitro a comparable antifungal activity to itraconazole. Plasma levels of hydroxy-itraconazole are about two times higher than those of itraconazole.

Excretion: After repeated oral administration, elimination of itraconazole from plasma is biphasic with a terminal half-life of 1.5 days. Fecal excretion of the parent drug varies between 3%-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 35% of the dose is excreted as metabolites in the urine within one week.

Special Populations and Conditions

Pediatrics: Limited pharmacokinetic data are available in pediatric patients (see *Product Monograph Part II: DETAILED PHARMACOLOGY - Human Pharmacokinetics*).

Geriatrics: No data are available in geriatric patients.

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 ± 18ng/mL, mean healthy C_{max} 164 ± 34 ng/mL) and a twofold 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 ± 207ng.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 \pm SD pharmacokinetic parameters are summarized in Table 1.3.

Table 1.3: 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 \pm 1.2	213 \pm 178	1026 \pm 819
Hemodialysis			
Off dialysis (7)	4.7 \pm 1.4	140 \pm 119	634 \pm 507
On dialysis (7)	4.1 \pm 0.9	113 \pm 83	507 \pm 371
CAPD (5)	4.4 \pm 2.2	77 \pm 29	325 \pm 107

Plasma concentration vs. time profiles showed wide inter-subject variation in all three groups. In uremic subjects (mean CrCl 13 mL/min/1.73m²), mean plasma concentrations and overall exposure, based on AUC_∞, were slightly reduced compared with healthy subject in a previous study (AUC_∞ values of 3454 \pm 3132 vs. 4161 \pm 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 1.3), 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.

Cystic Fibrosis: In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady-state dosing of oral solution using 2.5 mg/kg b.i.d. 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[®] oral solution, consideration should be given to switching to alternative therapy.

STORAGE AND STABILITY

SPORANOX[®] oral solution should be stored at 15°C - 25°C. Discard remaining unused product three months after opening bottle. Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Each millilitre of SPORANOX[®] oral solution contains 10 mg of itraconazole as well as: hydroxypropyl- β -cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour 1 and 2, caramel flavour, sodium saccharin, sodium hydroxide and purified water.

Dosage Forms and Packaging

SPORANOX[®] oral solution is available as a 10 mg itraconazole per mL solution, with 150 mL in each amber glass bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

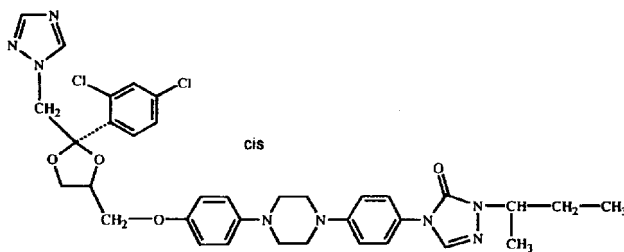
Drug Substance

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: C₃₅H₃₈Cl₂N₈O₄, 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.

CLINICAL TRIALS

Oropharyngeal Candidiasis

Table 2.1 - Summary of patient demographics for clinical trials in oropharyngeal candidiasis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (total/efficacy) ^a	Mean age (Range) ^b	Gender (M/F) ^b
ITR-USA-7	third-party blinded, active-controlled	itraconazole oral solution 200 mg o.d. for 7 days	n=64/60	38 (25-67)	56/8
		itraconazole oral solution 200 mg o.d. for 14 days	n=64/59	36.5 (21-67)	62/2
		fluconazole tablet 100 mg o.d. for 14 days	n=62/60	37.5 (24-61)	58/4
ITR-INT-27	multicentre, randomized, double-blind, double-dummy, active-controlled	itraconazole oral solution 100 mg b.i.d. for 7 days	n=79/68	37 (22-64)	72/7
		itraconazole oral solution 100 mg o.d. for 14 days	n=79/68	35 (24-58)	70/9
		fluconazole tablet 100 mg o.d. for 14 days	n=86/78	36 (21-66)	79/7
ITR-USA-94	uncontrolled, open-label	itraconazole oral solution, 100 mg b.i.d. for 14-28 days based on response	n=74/68	37 (20-60)	68/6

^a Total: intent-to-treat population; Efficacy: patients included in efficacy analysis

^b values based on total number of study subjects

Two randomized, controlled studies for the treatment of oropharyngeal candidiasis have been conducted. In one trial (n=179, all patients HIV-seropositive), clinical response (a global clinical evaluation of cured or improved) was not significantly different for patients treated with fluconazole tablets, 100 mg/day for 14 days (52/60; 87%), or itraconazole oral solution, 200 mg/day given for 7 days (50/60; 83%) or 14 days (57/59; 97%). Response to 14 days therapy with itraconazole oral solution was associated with a lower relapse rate than response to 7 days therapy with itraconazole oral solution. In the other trial (n=214, all HIV-seropositive patients), clinical response was not significantly different for patients treated with itraconazole oral solution 200 mg/day for 14 days, itraconazole oral solution 100 mg/day for 14 days or fluconazole 100 mg/day for 14 days. Response was 56/68 (84%), 62/68 (91%) and 71/78 (91%) for patients treated with a daily dose of itraconazole oral solution 200 mg, itraconazole oral solution 100 mg and fluconazole 100 mg, respectively.

In an uncontrolled, open-label study of selected patients clinically unresponsive to fluconazole tablets (n=74, all patients HIV-seropositive), patients were treated with itraconazole oral solution 100 mg b.i.d. (clinically unresponsive to fluconazole in this study was defined as having received a dose of fluconazole tablets at least 200 mg/day for a minimum of 14 days). Treatment duration was 14-28 days based on response.

The mean CD4 count of these patients was 23/mm³. Approximately 55% of patients had complete resolution of oral lesions. Of patients who responded and then entered a follow-up phase (n=22), all relapsed within a month when treatment was discontinued, with a median time to relapse of 14 days. Although baseline endoscopies had not been performed, several patients in this study developed symptoms of esophageal candidiasis while receiving treatment with itraconazole oral solution. Itraconazole oral solution has not been directly compared to other agents in a controlled trial of similar patients.

Esophageal Candidiasis

Table 2.2 - Summary of patient demographics for clinical trials in esophageal candidiasis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (total/efficacy) ^b	Mean age (Range) ^c	Gender (M/F) ^c
ITR-USA-12	double-blind, randomized, active-controlled	itraconazole oral solution 100-200 mg o.d. for 3-8 wks ^a	n=63/53	38 (24-57)	53/10
		fluconazole tablet 100-200 mg o.d.	n=63/57	37 (23-62)	55/8

^a Treatment continued for two weeks beyond resolution of symptoms, but not less than 3 weeks nor more than 8 weeks

^b Total: intent-to-treat population; Efficacy: patients included in efficacy analysis

^c values based on total number of study subjects

A double-blind, randomized study (n=110, 102 of whom were HIV-seropositive) compared itraconazole oral solution (100 mg/day) to fluconazole tablets (100 mg/day). The dose of each was increased to 200 mg/day for patients not responding initially. Treatment continued for 2 weeks following a resolution of symptoms for a total duration of 3-8 weeks. Clinical response (a global clinical assessment of cured or improved) was not significantly different between the two study arms and was >90% for both arms. Six of 53 (11%) itraconazole patients and 12 of 57 (21%) fluconazole patients were escalated to the 200 mg dose in this trial. Of the subgroup of patients who responded and entered a follow-up phase (n=88), approximately 23% relapsed across both arms within 4 weeks.

Oral and/or Esophageal Candidiasis

Table 2.3 - Summary of patient demographics for clinical trials in oral and/or esophageal candidiasis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (total/efficacy) ^a	Mean age (Range) ^b	Gender (M/F) ^b
ITR-FRA-5	uncontrolled, open-label	<u>Week 1-2:</u> itraconazole oral solution 100 mg b.i.d. <u>Week 3-4 in case of failure:</u> itraconazole oral solution 200 mg b.i.d.	n=60/40	38 (25-69)	50/10

^a Total: intent-to-treat population; Efficacy: patients included in efficacy analysis

^b values based on total number of study subjects

An uncontrolled, open-label study (n=40, all patients HIV-seropositive) treated patients clinically unresponsive or refractory to fluconazole tablets (defined as a dose of fluconazole tablets 100-200 mg/day for a minimum of 14 days) with itraconazole oral solution, 100 mg b.i.d. for 14 days. If not cured, itraconazole oral solution treatment was continued at 400 mg b.i.d. for another 14 days. Sixty percent of the evaluable patients had sufficient improvement at week 2; 70% of the patients were clinically cured at the end of treatment period.

DETAILED PHARMACOLOGY

Human 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 P-450 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 1 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 six 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 17 β -estradiol levels. The same dose taken during the luteal phase had no effects on 17 β -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 \pm 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 six 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 \pm 3.3% to 53 \pm 3.3%. This increase as well as shifts in the other immunological parameters remained within the normal ranges.

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.

Human Pharmacokinetics

Absorption

The absolute bioavailability of itraconazole administered as a non-marketed solution formulation under fed conditions was 55% in six healthy male volunteers. However, the bioavailability of SPORANOX[®] itraconazole oral solution is increased under fasted conditions reaching higher maximum plasma concentrations (C_{max}) in a shorter period of time. In 27 healthy male volunteers, the steady-state area under the plasma concentration versus time curve (AUC_{0-24}) of itraconazole (SPORANOX[®] oral solution, 200 mg daily for 15 days) under fasted conditions was 131 \pm 30% of that obtained under fed conditions. Therefore, unlike SPORANOX[®] capsules, it is

recommended that SPORANOX[®] oral solution be administered without food. Presented in Table 2.4 below are the steady-state (Day 15) pharmacokinetic parameters for itraconazole and hydroxy-itraconazole (SPORANOX[®] oral solution) under fasted and fed conditions.

Table 2.4 - Steady-state pharmacokinetic parameters for itraconazole and hydroxy-itraconazole under fasted and fed conditions.

	Itraconazole		Hydroxy-itraconazole	
	Fasted	Fed	Fasted	Fed
C _{max} (ng/mL)	1963 ± 601*	1435 ± 477	2055 ± 487	1781 ± 397
T _{max} (hours)	2.5 ± 0.8	4.4 ± 0.7	5.3 ± 4.3	4.3 ± 1.2
AUC ₀₋₂₄ (ng·h/mL)	29271 ± 10285	22815 ± 7098	45184 ± 10981	38823 ± 8907
t _{1/2} (hours)	39.7 ± 13	37.4 ± 13	27.3 ± 13	26.1 ± 10

*mean ± standard deviation

The bioavailability of SPORANOX[®] oral solution relative to SPORANOX[®] capsules was studied in 30 healthy male volunteers who received 200 mg of itraconazole as the oral solution and capsules under fed conditions. The AUC_{0-∞} from SPORANOX[®] oral solution was 149 ± 68% of that obtained from SPORANOX[®] capsules; a similar increase was observed for hydroxy-itraconazole. In addition, a cross-study comparison of itraconazole and hydroxy-itraconazole pharmacokinetics following the administration of single 200 mg doses of SPORANOX[®] oral solution (under fasted conditions) or SPORANOX[®] capsules (under fed conditions) indicates that when these two formulations are administered under conditions which optimize their systemic absorption, the bioavailability of the solution relative to capsules is expected to be increased further. Therefore, it is recommended that SPORANOX[®] oral solution and SPORANOX[®] capsules not be used interchangeably. Table 2.5 contains pharmacokinetic parameters for itraconazole and hydroxy-itraconazole following single 200 mg doses of SPORANOX[®] oral solution (n=27) or SPORANOX[®] capsules (n=30) administered to healthy male volunteers under fasted and fed conditions, respectively.

Table 2.5 - Pharmacokinetic parameters for itraconazole and hydroxy-itraconazole in healthy male volunteers under fed and fasted conditions

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

*mean ± standard deviation

HIV-Positive Patients:

The bioavailability of itraconazole oral solution was investigated in two groups of HIV-positive patients characterized by the severity of their HIV infection. The first group consisted of 12 patients with CD4 count $> 200/\text{mm}^3$ and no AIDS; the second group included 11 patients with CD4 count $< 100/\text{mm}^3$ and AIDS. At 100 mg b.i.d. for 15 days, both groups displayed satisfactory plasma concentrations and the bioavailability was equivalent in both groups. Table 2.6 summarizes the study results.

Table 2.6 - Plasma concentrations (ng/mL) of itraconazole and hydroxy-itraconazole after repeated administration of itraconazole oral solution in HIV-positive patients

Day	HIV-positive patients with CD4 count $> 200/\text{mm}^3$		AIDS patients with CD4 count $< 100/\text{mm}^3$	
	Itraconazole	Hydroxy-itraconazole	Itraconazole	Hydroxy-itraconazole
2	112 \pm 45*	310 \pm 121	95 \pm 84	258 \pm 156
4	305 \pm 93	771 \pm 211	271 \pm 189	688 \pm 346
7	443 \pm 189	1105 \pm 343	424 \pm 281	1034 \pm 524
13	585 \pm 250	1302 \pm 511	587 \pm 377	1339 \pm 731
15	645 \pm 303	1481 \pm 563	583 \pm 414	1355 \pm 800

*mean \pm standard deviation

Pediatric Patients:

The pharmacokinetics of SPORANOX[®] oral solution were studied in 26 pediatric patients requiring systemic antifungal therapy. Patients were stratified by age: 6 months to 2 years (n=8), 2 to 5 years (n=7) and 5 to 12 years (n=11), and received itraconazole oral solution 5 mg/kg once daily for 14 days. Pharmacokinetic parameters at steady state (Day 14) were not significantly different among the age strata and are summarized in Table 2.7 below for all 26 patients.

Table 2.7 - Pharmacokinetics of itraconazole oral solution in pediatric patients

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

*mean \pm standard deviation

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 five 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. 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 two to three times higher than the corresponding plasma concentration.

Metabolism and Excretion

Itraconazole is extensively metabolized by the liver into a large number of metabolites. One of the metabolites is hydroxy-itraconazole, which has antifungal activity comparable to itraconazole *in vitro*. Antifungal drug levels measured by bioassay were about three times those of itraconazole assayed by high-performance liquid chromatography. Fecal excretion of the parent drug varies between 3%-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. One week after oral administration of radiolabelled itraconazole, urinary excretion of total radioactivity amounted to 35% of the dose and fecal excretion represented 54% of the dose. 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.

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 ^3H -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 6 days in rats and rabbits and within 14 days 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 two to five times higher than the corresponding plasma levels. Lowest levels at any time point occurred in the blood and brain.

Brain to plasma ratios were about 1. 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 three species. There were some quantitative differences for the mass balance of the metabolites in the three 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.*, *Malassezia spp.* and *Cryptococcus neoformans*), dimorphic fungi (e.g. *Histoplasma*, *Paracoccidioides brasiliensis*, *Blastomyces dermatitidis* and *Sporothrix schenckii*), various organisms which cause chromomycosis, and other fungi including *Aspergillus fumigatus*.

MIC₉₀'s for the majority of medically important fungi are between 0.1 and 1.0 $\mu\text{g/mL}$, while fungicidal activity is obtained at higher concentrations (10 $\mu\text{g/mL}$). 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 2.8.

Table 2.8 - 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	100	
<i>Candida albicans</i>	1	1401	0.2	8.6	71.0	98.1	99.8		
Other <i>Candida spp.</i>	17	267	1.9	22.5	87.6	98.1	99.6	100	
<i>Torulopsis spp.</i>	5	245	1.2	10.6	87.3	97.6	99.6	100	
<i>Cryptococcus neoformans</i>	1	33	3	60.6	100	-			
<i>Pityrosporum ovale</i> ¹	1	35	0	0	91.4	100			
Various yeasts	6	55	20	47.3	72.7	92.7	96.4	100	
<i>Aspergillus fumigatus</i>	1	83	0	7.2	68.7	98.8	100		
Various <i>Aspergillus</i> & <i>Penicillium spp.</i>	19	57	1.8	3.5	63.2	80.1	93.0	100	
<i>Sporothrix schenckii</i>	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			
Enfungi (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 in vivo activity of oral itraconazole observed in experimental animal models of systemic mycoses is shown in Table 2.9. 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.

Table 2.9 - In vivo activity of 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 Survived 21 days Negative kidney culture
	Rat	0/3		100							
	Rabbit	+1/7							86 ^b		
Aspergillosis	Guinea pig	0/14			83	75					Survived 28 days Survived 28 days Survived 28 days Survived 28 days Negative kidney culture Cured
	Guinea pig	+0/14			50	83					
	IC ^d guinea pig	0/28			100						
	IC ^d guinea pig	+1/28			80						
	Mouse	0/5							47		
	Rabbit ^c	+3/14			100						
Cryptococcosis	Guinea pig	+3/35				88	100				Negative culture (CSF excluded) Negative CSF culture Negative CSF culture
	Mouse	0/14							53		
	Rabbit	+4/14							73 ^b		
Sporotrichosis	Guinea pig	0/28					80	100			Cured
Histoplasmosis	Guinea pig	0/14				63		100			Cured
Coccidioidomycosis	Rat	- 3/14					100 ^e				Negative lung culture
	Rat	+7/14					80 ^e				Negative lung culture
Paracoccidioidomycosis	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.

Development of Resistance and Cross-Resistance to Itraconazole

A three-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 IC₅₀ 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

Single-Dose Toxicity

Itraconazole/(HP- β -CD) was administered orally and intravenously to mice, rats and dogs from both genders. The results are summarized in Table 2.10.

Table 2.10 - Single-Dose Toxicity Studies with Itraconazole/(HP- β -CD)

Species	Route	Sex	LD ₅₀ -values (mg itraconazole/(HP- β -CD)/kg bwt)
mouse	oral	M & F	> 100/(2500)
mouse	intravenous	M & F	> 44.1/(1764)
rat	oral	M & F	> 100/(2500)
rat	intravenous	M & F	> 17.6/(704)
dog	oral	M & F	> 100/(2500)
dog	intravenous	M & F	> 17.6/(704)

Upon oral administration, all animals survived the maximum dose of 100/(2500) mg/kg body weight (bwt). Clinical responses mainly consisting of soft feces or diarrhea were seen in all three species. As they were also present in the mice and rats dosed with HP- β -CD alone, these phenomena were considered to be due to the osmotic effects of HP- β -CD.

A single intravenous dose of 44.1/(1764) mg/kg bwt in mice and 17.6/(704) mg/kg bwt in rats and dogs did not result in mortality. Clinical effects observed were transient hyperpnea in rats and mice, and dyspnea and loss of righting reflex in dogs. These effects were only seen during the first hours after injection.

Long-Term Toxicity

For the evaluation of repeated oral use of itraconazole/(HP- β -CD), mice, rats and dogs were daily dosed for 3 months. In addition, chronic oral toxicity studies were performed in rats (6 months) and dogs (12 months). The duration of these studies was done in conformity with the requirements of the major regulatory authorities worldwide.

Table 2.11 - Doses of itraconazole/(HP- β -CD) in studies in mice, rats and dogs

Study	itraconazole/(HP- β -CD) doses in mg/kg bwt
3 month pilot toxicity in mice	0/(0), 0/(800), 5/(200), 20/(800), 80/(3200)
3 month toxicity in rats	0/(0), 0/(4000), 5/(1000), 20/(2000), 80/(4000)
6 month toxicity in rats	0/(0), 0/(800), 5/(200), 20/(800), 30/(0)
3 (+1)* month toxicity in dogs	0/(500), 5/(300), 10/(400), 20/(500)
12 month toxicity in dogs	0/(0), 0/(800), 5/(200), 20/(800), 20/(0)

* +1 month of recovery

In the studies performed with itraconazole/(HP- β -CD) in mice, rats and dogs, the itraconazole dose of 5 mg/kg body weight was virtually not toxic. In rats, the only effects observed were, as expected from the toxicological profile of itraconazole, slightly increased serum cholesterol and phospholipid-levels, and minimal histological changes of the adrenal cortex (swelling), but without any cytopathological changes. In dogs, slight histological changes of the mononuclear

phagocytosing system (MPS) mainly consisting of an increase in foamy macrophages and adaptive changes in the urinary tract (swelling and vacuolation of epithelial cells in the renal pelvis and the urinary bladder) were the only effects observed, and they were mainly attributable to HP- β -CD.

In mice, dosing at 20/(800) and 80/(3200) mg/kg for 3 months resulted in slight to more pronounced toxicity. Serum aspartate and alanine aminotransferase levels were elevated, and at 80/(3200) mg/kg, associated with histological liver changes (eosinophilic aspect of hepatocytic cytoplasm and increase in individual cell necrosis). Histological examination further revealed modifications of the adrenal cortex (swelling) at 80/(3200) mg/kg bwt. In addition, HP- β -CD-related adaptive changes of the urinary tract were noted at 20/(800) and 80/(3200) mg/kg bwt.

In rats dosed for 3 months, 20/(2000) and 80/(4000) mg/kg bwt were moderately toxic doses. At these doses, target organs or tissues were similar to those observed with itraconazole alone, i.e. the adrenal cortex, the liver, the MPS, and the ovaries. Increased serum cholesterol and phospholipid-levels were also observed. Changes related to the HP- β -CD-vehicle were slightly decreased hematocrit and hemoglobin, a slightly lowered number of red blood cells, and adaptive changes of urinary bladder and renal pelvis.

Dosing in rats for 6 months at 20/(800) mg/kg and at 30/(0) mg/kg, a dose of itraconazole in PEG resulting in a similar systemic exposure, revealed toxicity mainly characterized by some altered blood and serum variables, and histological changes in MPS, liver and adrenal cortex. HP- β -CD-related effects in the 20/(800) and the 0/(800) mg/kg dosed groups were limited to histological changes in urinary tract and to an increased pancreas weight, but without apparent histological changes.

In dogs dosed for 3 months, itraconazole-related toxicity at 10/(400) and 20/(500) mg/kg bwt was confined to a slightly decreased body weight gain, some altered blood and serum variables, a slightly increased adrenal weight and foci of foamy cells in the lungs. The latter finding was also seen in the 0/(500)-vehicle dosed group, indicating that it is at least partially related to HP- β -CD.

Oral administration of HP- β -CD further led to slightly decreased hematocrit and hemoglobin and a slightly lowered number of red blood cells. After 1 month of recovery, the changed parameters in the 0/(500) and 20/(500) mg/kg dosed groups showed good reversibility.

Repeated dosing at 20/(800) or 20/(0) mg/kg for 12 months mainly produced reduced body weight gain and some changed blood and serum variables. At these doses, histological examination revealed itraconazole-related effects on the MPS and the adrenal cortex. Apart from transient softening of the stools and adaptive urinary tract changes, no other HP- β -CD-related effects were present.

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

Itraconazole was administered in the diet for 23 months to groups of 50 male and 50 female mice and for 24 months to groups of 50 male and 50 female rats in order to evaluate its carcinogenic potential.

In mice, itraconazole showed no evidence of carcinogenicity potential at oral dosage levels up to 80 mg/kg/day (approximately 10x the maximum recommended human dose (MRHD)).

However, female mice receiving 80 mg/kg/day displayed a temporary body weight decrease and an increased incidence of adrenal pigmentation.

Female rats treated with itraconazole at 50 mg/kg/day (6.25xMRHD), had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increased incidence in this study was not statistically significant. Male rats treated with 25 mg/kg/day (3.1xMRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcoma 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.

Hydroxypropyl- β -cyclodextrin (HP- β -CD), the solubilizing excipient used in SPORANOX[®] oral solution, was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months. The likely mechanism is that oral administration of HP- β -CD resulted in a cholecystokinin (CCK)-mediated increase in hyperplasia of the acinar cells in the exocrine pancreas. This rat-specific finding was not

observed in the mouse carcinogenicity study at doses 500, 2000 or 5000 mg/kg/day for 22-23 months.

Excipient: Hydroxypropyl- β -Cyclodextrin (HP- β -CD)

HP- β -CD is a new carrier molecule designed to enhance oral absorption and exposure to drugs. Chemically, it is a cyclic oligosaccharide built up from 7 glucopyranose units with 4.06 to 5.11 hydroxypropyl groups per molecule of cyclodextrin.

Pharmacodynamic studies have shown that HP- β -CD has no intrinsic in vivo pharmacological activities that might hinder its presence in the clinical formulation of itraconazole oral solution. No interactions between HP- β -CD and drugs are expected from either a pharmacodynamic or a metabolic point of view.

The pharmacokinetics of HP- β -CD after both intravenous and oral administration are similar in experimental animals and man. Intravenously dosed HP- β -CD is cleared very rapidly from the plasma, mainly by renal excretion of the intact compound. In animals, the tissue distribution is limited, and highest concentrations are measured in the urinary tract. The systemic absorption after oral administration of intact HP- β -CD is low. HP- β -CD is excreted for 50% - 62% of the dose as the intact compound in the feces. The bulk of the remaining part is metabolized by the intestinal microflora, and the absorption and tissue distribution of the biodegradation products are limited too. After oral dosing, the gastrointestinal tissues show the highest exposure to intact HP- β -CD as well as its biodegraded products. In view of the limited systemic absorption of HP- β -CD after oral administration, a stimulant effect on intestinal secretion and motility after high oral doses from 1500 mg/kg bwt onwards can be expected.

Single dose toxicity studies in mice, rats and dogs indicate a wide safety margin after oral and intravenous administration of HP- β -CD. In the (sub)chronic toxicity studies, most effects were of an adaptive nature (histological changes in the urinary tract, softening of feces, activation of the MPS) and showed good reversibility. Slight, reversible liver changes occurred at doses of about 30 times the proposed human dose of HP- β -CD in the itraconazole oral solution. HP- β -CD has no antifertile, no direct embryotoxic and no teratogenic effect. The chemical structure of HP- β -CD does not raise suspicion for genotoxic activity either. Tests on DNA-damage, gene mutations and chromosome aberrations in vitro and in vivo did not reveal any genotoxic activity of HP- β -CD.

In the rat study, an increased incidence of neoplasms in the large intestine and in the exocrine pancreas was seen. The slightly higher incidence of adenocarcinomas in the large intestine was observed at 5000 mg/kg. The increased incidence was linked to the hypertrophic/hyperplastic and inflammatory changes in the colonic mucosa brought about by the HP- β -CD-induced increased osmotic forces. There is no evidence of HP- β -CD per se exerting a tumorigenic effect on the large intestine. Hyperplasia and neoplasia of the exocrine pancreas, related to the mitogenic action of CCK, were only seen in those studies where HP- β -CD was given orally to rats (see **TOXICOLOGY, Carcinogenicity**). The clinical relevance of these findings is unknown. In addition, chronic administration of HP- β -CD for 12 months to dogs (up to 2000 mg/kg bwt with eight dogs in each group) or to female cynomolgus monkeys for 2 years (800/400 mg/kg bwt, 13 monkeys per group) did not cause hyperplastic/neoplastic pancreatic changes.

REFERENCES

1. Blatchford NR. Treatment of oral candidosis with itraconazole: a review. 2nd International Symposium on Itraconazole, Antwerp, Belgium, June 22-23, 1989. *Journal of the American Academy of Dermatology* 1990;23(3)(Part 2):565-567.
2. Borgers M, Van de Ven MA. Mode of action of itraconazole: morphological aspects. *Mycoses* 1989;32(Suppl 1):53-60.
3. Cauwenbergh G, De Doncker P, Stoops K, De Dier A, Goyvaerts H, Schuermans V. Itraconazole in the treatment of human mycoses: Review of three years of clinical experience. *Reviews of Infectious Diseases* 1987;9(Suppl 1):S146-S152.
4. De Repentigny L, Ratelle J, and the HIVIK Project Group. Itraconazole (I) vs ketoconazole (K) in HIV-positive patients with oropharyngeal and/or esophageal Candidiasis. 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, California, USA, October 11-14, 1992.
5. Dupont B, Drouhet E. Early experience with itraconazole in vitro and in patients: pharmacokinetic studies and clinical results. *Reviews of Infectious Diseases* 1978;9: S71-76.
6. Grant SM, Clissold SP. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in superficial and systemic mycoses. *Drugs* 1989;37:310-344.
7. Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn JG. Pharmacokinetics of itraconazole following oral administration to normal volunteers. *Antimicrobial Agents and Chemotherapy* 1988;32(9):1310-1313.
8. Heykants J, Michiels M, Meuldermans W, et al. The pharmacokinetics of itraconazole in animals and man: an overview. In: R.A. Fromtling, J.R. ed. *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*. Prous Science Publishers, S.A., 1987;223-249.
9. Heykants J, Van Peer A, Van de Velde V, et al. The clinical pharmacokinetics of itraconazole: an overview. *Mycoses* 1989;32(Suppl 1):67-87.
10. Moreno F, Hardin TC, Rinaldi MG, Graybill JR. Itraconazole-didanosine excipient interaction. *Journal of the American Medical Association* 1993;269:1508.
11. Phillips P, Zemcov J, Mahmood W, et al. Itraconazole cyclodextrin solution for fluconazole-refractory oropharyngeal candidiasis in AIDS: correlation of clinical response with in vitro susceptibility. *AIDS* 1996;10:1369-1376.
12. Restrepo A, Gonzalez A, Gomez I, Arango M, De Bedout C. Treatment of chromoblastomycosis with itraconazole. First International Conference on Drug Research in Immunologic and Infectious Diseases: Antifungal Drugs: Synthesis, Preclinical and Clinical Evaluation, New York, October 8-10, 1987. *Annals of the New York Academy of Sciences* 1988;544:504-516.
13. Smith DE, Midgely J, Allan M, Connolly GM, Gazzard BG. Itraconazole versus ketoconazole in the treatment of oral and oesophageal candidosis in patients infected with HIV. *AIDS* 1991;5:1367-1371.

14. Tucker RM, Williams PL, Arathoon EG, Stevens DA. Treatment of mycoses with itraconazole. *Annals of the New York Academy of Sciences* 1988;544:451-470.
15. Van Cauteren H, Coussement W, Vandenberghe J, Herin V, Vanparys PH, Marsboom R: The toxicological properties of itraconazole. In: R.A. Fromtling, J.R. ed. *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*. Prous Science Publishers, S.A. 1987;263-271.
16. Van Cutsem J. Oral, topical and parenteral antifungal treatment with itraconazole in normal and in immunocompromised animals. *Mycoses* 1989;32(Suppl 1):14-35.
17. Van Cutsem J. The in-vitro antifungal spectrum of itraconazole. *Mycoses* 1989;32 (Suppl 1):7-14.
18. Van Cutsem J, Van Gerven F, Janssen PAJ. The in vitro and in vivo antifungal activity of itraconazole. In: R.A. Fromtling J.R., et al. eds. *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*. Telesymposia proceedings. Prous Science Publishers, Barcelona, 1987.
19. Vanden Bossche H, Marichal P, Gorrens J, et al. Biochemical approaches to selective antifungal activity. Focus on azole antifungals. *Mycoses* 1989;32(Suppl 1):35-53.
20. Van de Velde Vera JS, Van Peer Achiel P, Heykants Joseph JP, et al. Effect of Food on the Pharmacokinetics of a New Hydroxypropyl- β -Cyclodextrin Formulation of Itraconazole. *Pharmacotherapy* 1996;16(3):424-428.
21. Warnock DW, Turner A, Burke J. Comparison of high performance liquid chromatographic and microbiological methods for determination of itraconazole. *Antimicrobial Agents and Chemotherapy* 1988;21:93-100.

PART III: CONSUMER INFORMATION

PrSPORANOX®* itraconazole oral solution

This leaflet is part III of a three-part "Product Monograph" published when SPORANOX® oral solution 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® oral solution. Contact your doctor or pharmacist if you have any questions about the drug.

This information is for patients who have been prescribed SPORANOX® oral solution for treatment of fungal infections of the mouth and throat. 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 medicine used to treat fungal infections of the mouth and throat in adult HIV-positive patients or other patients with a lowered immune system.

This Consumer Information discusses only the oral solution form of SPORANOX®. You will receive the oral solution in a glass bottle, containing 150 mL of solution (10 mg itraconazole per millilitre solution), along with a measuring cup.

What it does:

SPORANOX® goes into your bloodstream and travels to the area of the infection.

When it should not be used:

- if you have congestive heart failure, SPORANOX® could make it worse. If your doctor decides that you need SPORANOX®, be sure to get immediate medical help if you experience signs of heart failure (see **SERIOUS 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® oral solution (see **What the nonmedicinal ingredients are**)

What the medicinal ingredient is:

The medicinal ingredient in SPORANOX® oral solution is itraconazole. One full measuring cup contains 10 millilitres of solution, corresponding to 100 milligrams of itraconazole.

What the nonmedicinal ingredients are:

SPORANOX® oral solution contains: hydroxypropyl-β-cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour 1 and 2, caramel flavour, sodium saccharin, sodium hydroxide and water.

What dosage forms it comes in:

Oral Solution 10 mg/mL

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Liver toxicity (see **SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM**)
- Cardiac toxicity (see **SERIOUS SIDE EFFECTS 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® oral solution because they may have certain health problems or may be taking certain medicines that could lead to serious or life-threatening medical problems.

Tell your doctor about any other medical conditions you have had, especially heart, lung, liver or kidney conditions. Also tell your doctor and pharmacist the name of all the prescription and non-prescription medicines you are taking, including dietary supplements and herbal remedies.

BEFORE you use SPORANOX® let your doctor or pharmacist know if:

- you have elevated or abnormal liver enzymes or active liver disease, or have experienced liver toxicity with other drugs;
- you have or have had heart disease, including congestive heart failure;
- you have ever had an allergic reaction to itraconazole or any of the other ingredients in SPORANOX® oral solution.

Do not take SPORANOX® oral solution 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, you should use effective birth control during SPORANOX® treatment and for 2 months after finishing treatment. Ask your doctor about effective types of birth control.

Do not take SPORANOX® oral solution if you are breast-feeding or discontinue nursing if you are taking SPORANOX®.

Since scientific information on the use of SPORANOX® oral solution in children is limited, it is not recommended for use in children.

INTERACTIONS WITH THIS MEDICATION

A wide variety of drugs may interact with SPORANOX[®] oral solution. Do not take SPORANOX[®] oral solution if you are taking any of the following medications.

- quinidine (such as Cardioquin[®], Quinidex[®]), dofetilide[‡], levacetylmethadol[‡] (levomethadyl), cisapride[‡] and pimozide (such as Orap[®]) which could result in dangerous or even life-threatening abnormal heartbeats, eletriptan (such as Relpax[®]), a migraine medication, which could result in serious side effects
- HMG - CoA reductase inhibitors such as lovastatin (Mevacor[®]) and simvastatin (Zocor[®]) which could result in potentially serious breakdown of muscle tissue
- triazolam (such as Halcion[®]) and midazolam (such as Versed[®]) which may worsen or prolong drowsiness
- ergot alkaloids such as dihydroergotamine, ergotamine and ergometrine (ergonovine) and methylergometrine[‡] (methylergonovine) which could result in a serious or life-threatening decrease in blood flow to the brain and/or limbs (ischemia).
- nisoldipine[‡], a medicine for angina or high blood pressure.

Other medications may also interact with SPORANOX[®] oral solution. These include:

- fentanyl and alfentanil, strong medicines for pain
- carbamazepine, phenytoin and phenobarbital, drugs used to treat epilepsy
- rifampicin, rifabutin, isoniazid, clarithromycin and erythromycin, drugs to treat infections
- digoxin, disopyramide, cilostazol[‡] and calcium channel blockers (such as nifedipine, felodipine and verapamil), drugs that act on the heart and blood vessels
- warfarin, a drug that slows down blood clotting
- budesonide, dexamethasone, fluticasone and methylprednisolone, drugs for inflammation, asthma and allergies
- some drugs used to treat AIDS/HIV known as protease inhibitors and nevirapine
- busulfan, docetaxel and vinca alkaloids, drugs used in cancer treatment
- alprazolam, diazepam and buspirone, drugs to help you sleep or to treat anxiety
- atorvastatin and cerivastatin[‡], drugs used to lower cholesterol
- drugs taken orally to treat diabetes such as repaglinide
- trazodone, a drug used to treat depression
- trimetrexate, a drug for serious pneumonia
- cyclosporine, tacrolimus and sirolimus, drugs which are usually given after an organ transplant
- halofantrine[‡], a drug used to treat malaria.

[‡] not marketed in Canada

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

PROPER USE OF THIS MEDICATION

You should always take SPORANOX[®] oral solution without food. You should not eat or drink for one hour after taking SPORANOX[®] oral solution.

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

Do not switch to SPORANOX[®] capsules without talking to your doctor.

Usual dose:

Your doctor will decide the right dose for you. Depending on your infection, you will take SPORANOX[®] oral solution once or twice a day for as long as prescribed by your doctor.

Use the dosing cup provided in your SPORANOX[®] package to accurately measure the amount of solution needed. SPORANOX[®] oral solution should be poured into the end of the cup containing markings which indicate dosing amounts (2.5 mL, 5 mL and 10 mL). There are arrows on the sides of the dosing cup showing you which end to pour the solution into. You should swish the solution around in your mouth for approximately 20 seconds before swallowing it, and avoid rinsing your mouth after taking it.

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[®] oral solution, 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, headache, dizziness, menstrual disorders, erectile dysfunction, muscle weakness or pain, painful joints, unpleasant taste, oversensitivity to sunlight, hair loss, inflammation of the pancreas, and fever.

Report any side effects to your doctor or pharmacist.

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

Symptom / effect <i>The following side effects are all uncommon:</i>	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			
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 or numbness in hands or feet		✓	
Oversensitivity			
Skin rash			✓
Itching			✓
Hives			✓
Difficulty breathing or shortness of breath and/or swelling of the face			✓
Other			
Blurry or double vision		✓	
Ringing in ears		✓	
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[®] oral solution, contact your doctor or pharmacist.

HOW TO STORE IT

Keep all medicines, including SPORANOX[®] oral solution, out of the reach of children.

Store SPORANOX[®] oral solution at room temperature (15°C - 25°C). This medicine can be kept for only a limited time. Discard any remaining unused SPORANOX[®] oral solution three months after opening the bottle.

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 0701D
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

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