Product Monograph

Including Patient Medication Information

PrSPORANOX®

itraconazole
capsules
For oral use
100 mg
Antimycotic for systemic use, triazole and tetrazole derivatives
ATC code: J02A C02

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* a Johnson & Johnson company

Recent Major Label Changes

None at time of the most recent authorization	

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

SPORANOX (itraconazole) is indicated for:

- the treatment of the following systemic fungal infections in normal, predisposed or immunocompromised patients:

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

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

- the treatment of the following topical fungal infections in normal, predisposed or immunocompromised patients:

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

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

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

1.1. Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SPORANOX in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3. Pediatrics).

1.2. Geriatrics

Geriatrics (> 65 years of age): Clinical data on the use of SPORANOX in elderly patients is limited. It is advised to use SPORANOX in these patients only if it is determined that the potential benefit outweighs the potential risks (see 7.1.4. Geriatrics).

2. Contraindications

- SPORANOX should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see Table 1, Calcium Channel Blockers; 3. Serious Warnings and Precautions Box ; 7. Warnings and Precautions, Cardiovascular, Use in Patients with Underlying Cardiac Disease; 8.5. Post-Market Adverse Reactions).

- Coadministration with SPORANOX, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, causes increased plasma concentrations of drugs metabolized by this pathway which may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Drugs that are contraindicated in combination with itraconazole are listed in Table 1 (see 3. Serious Warnings and Precautions Box and 9.4. Drug-Drug Interactions, Table 6).

Table 1: Drugs that are contraindicated with SPORANOX

Drug Class	Drugs within Class that are Contraindicated with SPORANOX
Analgesics	methadone
Anti-arrhythmics	disopyramide, dronedarone, quinidine
Anticoagulants and Antiplatelet Drugs	ticagrelor, apixaban, rivaroxaban
Antifungals	isavuconazole
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, eletriptan
Antineoplastics	irinotecan, venetoclax (for chronic lymphocytic leukemia/small lymphocytic lymphoma patients during initiation/titration/ramp-up phase).
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, pimozide, triazolam
Antivirals	asunaprevir (boosted)
Calcium Channel Blockers	felodipine
Cardiovascular Drugs,	ivabradine, ranolazine
Diuretics	eplerenone
Gastrointestinal Drugs	domperidone, naloxegol
Lipid Regulating Drugs	lomitapide, lovastatin, simvastatin
Urologic Drugs	fesoterodine, in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment solifenacin, in subjects with severe renal impairment or moderate to severe hepatic impairment.
Miscellaneous Drugs and Other Substances	colchicine, in subjects with renal or hepatic impairment, eliglustat.

- SPORANOX are contraindicated in patients with a known hypersensitivity to itraconazole or its excipients. For a complete listing, see the 6. Dosage Forms, Strengths, Compositions, and Packaging .
- There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX to patients with hypersensitivity to other azoles.

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

3. Serious Warnings and Precautions Box

- **Congestive Heart Failure (CHF):** SPORANOX should not be administered to patients with evidence of ventricular dysfunction such as CHF or a history of CHF except for the treatment of life-threatening or other serious infections. If signs or symptoms of CHF occur during administration of SPORANOX, discontinue administration (see 2. Contraindications, Table 1, Calcium Channel Blockers; 7. Warnings and Precautions, Cardiovascular, Use in Patients with Underlying Cardiac Disease; 8.5. Post-Market Adverse Reactions).

Drug Interactions: Coadministration of a number of CYP3A4 substrates with SPORANOX is contraindicated. Drugs that are contraindicated are listed in Table 1 (see 2. Contraindications and 9.1. Serious Drug Interactions and 9.4. Drug-Drug Interactions, Table 6 The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

- Table 6).

- **Liver Toxicity:** SPORANOX has been associated with rare cases of serious hepatotoxicity, including liver failure and death. 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. (see 7. Warnings and Precautions, Hepatic/Biliary/Pancreatic and 8. Adverse Reactions).

4. Dosage and Administration

4.1. Dosing Considerations

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

SPORANOX capsules are a different preparation than itraconazole oral solution and should not be used interchangeably.

For maximal absorption, it is essential to administer SPORANOX immediately after a full meal (see 10. Clinical Pharmacology). See 7. Warnings and Precautions for treatment of patients with decreased gastric acidity.

Concomitant administration of SPORANOX with certain medications may require a dose adjustment for either SPORANOX or for the other medication (see 9. Drug Interactions).

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

Special Populations
Pediatrics (< 18 years of age)
Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

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

Patients with Hepatic Impairment
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population (see 7. Warnings and Precautions, Hepatic/Biliary/Pancreatic; 10. Clinical Pharmacology, Special populations and conditions, Hepatic Insufficiency).

Patients with Renal Impairment
Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered (see 7. Warnings and Precautions, Renal; 10. Clinical Pharmacology, Special populations and conditions, Renal Insufficiency).

4.2. Recommended Dose and Dosage Adjustment

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

Oral Candidiasis:
The recommended dose is 100 mg daily for 2 weeks.

Esophageal Candidiasis:
The recommended dose is 100 mg daily for 4 weeks.

Blastomycosis and Chronic Pulmonary Histoplasmosis
The recommended dose is 200 mg once daily. If there is no obvious improvement or there is evidence of progressive fungal disease, the dose should be increased in 100 mg increments to a maximum of 400 mg daily. Doses above 200 mg per day should be given in 2 divided doses.

Treatment should be continued for a minimum of 3 months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Other Systemic Mycoses
Table 2: Dosing recommendations for other systemic mycoses

Indication	Dose	Median Duration

Aspergillosis Pulmonary Invasive pulmonary	 200 mg o.d. 200 mg b.i.d.	 3-4 months 3-4 months
Sporotrichosis: lymphocutaneous and cutaneous	100 mg or 200 mg once daily (localized lesions) or 200 mg twice daily (extensive lesions)	3-6 months
Paracoccidioidomycosis	100 mg o.d.	6 months
Chromoblastomycosis (formerly chromomycosis) due to *Fonsecaea pedrosoi* due to *Cladosporium carrioni*	200 - mg o.d.	6 months

Dermatomycoses
Standard Dosages:
Tinea corporis/Tinea cruris
The recommended dose is 100 mg once daily for 14 consecutive days.

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

Pityriasis versicolor
The recommended dose is 100 mg twice daily or 200 mg once daily for 5-7 consecutive days.

Alternative Dosages:
Shorter dosing schedules have also been found to be effective in the treatment of *tinea corporis/tinea cruris* and *tinea pedis*. The shorter dosages are:
Tinea corporis/tinea cruris: 200 mg o.d. for 7 consecutive days;
Tinea pedis: 200 mg b.i.d. for 7 consecutive days.

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

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

Table 3: Recommended clinical dose for onychomycosis

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

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

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

4.4. Administration

SPORANOX capsules must be swallowed whole.

4.5. Missed Dose

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

5. Overdose

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

Although no data are available for SPORANOX, standard supportive treatment should be applied as necessary.

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

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 4: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	capsule 100 mg	D&C Red No. 22 (eosine), D&C Red No. 28 (phloxine B), FD&C Blue No. 1 (brilliant blue), FD&C Blue No. 2 (indigotin), gelatin, Hypromellose, macrogol and sugar spheres (NF) (composed of maize starch, purified water, and sucrose), and titanium dioxide.

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

SPORANOX is supplied in HDPE bottles of 30 capsules.

7. Warnings and Precautions

See 3. Serious Warnings and Precautions Box .

General

SPORANOX capsules and itraconazole oral solution should not be used interchangeably**.** This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. In addition, the topical effects of mucosal exposure may be different between the two formulations. Itraconazole oral solution is indicated only for the treatment of oral and/or esophageal candidiasis.

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

In systemic candidiasis, if fluconazole-resistant strains of *Candida* species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence it is recommended to have their sensitivity tested before the start of itraconazole therapy (see 15. Microbiology, Resistance and Cross-Resistance).

Carcinogenesis and Genotoxicity

See 16. Non-Clinical Toxicology, Carcinogenicity for discussion on animal data.

Cardiovascular

Cardiac Dysrhythmias

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as methadone, pimozide or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated (see 2. Contraindications and 9.1. Serious Drug Interactions and 9.4. Drug-Drug Interactions, Table 6 The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).
Table 6).

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 should not be administered for the treatment of onychomycosis or dermatomycoses in patients with evidence of ventricular dysfunction such as CHF or a history of CHF. SPORANOX should not be used for other indications in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk.

The benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g., total daily dose), and the individual risk factors for CHF. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, treated with caution, and monitored for signs and symptoms of CHF during treatment; if such

signs or symptoms do occur during treatment, SPORANOX should be discontinued (see 9. Drug Interactions and 8.5. Post-Market Adverse Reactions).

Itraconazole has been shown to have a negative inotropic effect. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study (n=8) of SPORANOX for injection, a transient asymptomatic decrease of the left ventricular ejection fraction was observed using gated SPECT imaging; this resolved before the next infusion, 12 hours later.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of SPORANOX with felodipine is contraindicated.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections (see 8.5. Post-Market Adverse Reactions).

Driving and Operating Machinery
Adverse reactions such as dizziness, visual disturbances and hearing loss have been reported while taking SPORANOX. These adverse reactions may impair the ability to drive a vehicle and operate machinery. While taking SPORANOX, patients should be cautioned not to drive, operate dangerous machinery or engage in activities that require alertness or physical coordination if they are experiencing any of these effects (see 8.5. Post-Market Adverse 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 2. Contraindications and 9. Drug Interactions, Antiarrhythmics). The hearing loss usually resolves when treatment is stopped but can persist in some patients.

Gastrointestinal
Use in Patients with Decreased Gastric Acidity
Absorption of itraconazole from SPORANOX is impaired when gastric acidity is decreased. In patients with reduced gastric acidity, whether from disease (e.g., patients with achlorhydria) or from concomitant medication (e.g., AIDS patients taking drugs that reduce gastric acidity), it is advisable to administer SPORANOX with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary (see 10.3. Pharmacokinetics, Absorption).

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

Hepatic/Biliary/Pancreatic
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 is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. Liver function monitoring should be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications and should be considered in all patients receiving SPORANOX.

Treatment should be stopped immediately, and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction. Such signs and symptoms include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, abdominal pain, dark urine or pale stools (see 3. Serious Warnings and Precautions Box and 8. Adverse Reactions).

Itraconazole binds extensively to plasma proteins.

Use in Patients with Hepatic Insufficiency
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population. It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. In a clinical trial in cirrhotic patients, the mean terminal half-life of itraconazole was increased by 131% and its mean C_{max} decreased by 47%. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolized by CYP3A4 (see 10. Clinical Pharmacology, Special populations and conditions, Hepatic Insufficiency).

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

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

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

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 100 mg b.i.d., showed that the pharmacokinetics of zidovudine were not affected during concomitant administration of SPORANOX.

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

Monitoring and Laboratory Tests

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

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

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

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

Neurologic

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

Renal

Use in Patients with Renal Insufficiency

Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered (see 10. Clinical Pharmacology, Special populations and conditions, Renal Insufficiency).

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

Itraconazole cannot be removed by hemodialysis.

Respiratory

Cystic Fibrosis

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

7.1. Special Populations

7.1.1. Pregnancy

SPORANOX should not be used for the treatment of onychomycosis or dermatomycoses in pregnant patients or in women contemplating pregnancy (see 2. Contraindications). SPORANOX must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the fetus. Itraconazole has been shown to produce teratogenic effects (major skeletal and secondary soft tissue defects) when administered at high doses (40 mg/kg/day, 5 times MRHD or higher) to pregnant rats. When administered to pregnant mice at high doses (80 mg/kg/day, 10 times MRHD or higher) itraconazole has been shown to produce encephaloceles and/or macroglossia.

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

Pregnancy should be avoided in women using SPORANOX and for 2 months following end of treatment. In women of childbearing potential, a reliable method of barrier contraception must always be used in combination with other methods of contraception e.g. oral or other hormonal contraceptives (see 9. Drug Interactions).

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 has not been established.

7.1.2. Breastfeeding

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

7.1.3. Pediatrics

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SPORANOX in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

No pharmacokinetic data are available in pediatric patients. A small number of patients from age 3 to 16 years have been treated with 100 mg/day of itraconazole for systemic fungal infections and no serious adverse events have been reported. Toxicological studies have shown that itraconazole, when administered to rats, can produce bone toxicity. While no such toxicity has been reported in adult patients, the long-term effect of itraconazole in children is unknown (see 16. Non-Clinical Toxicology).

7.1.4. Geriatrics

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

8. Adverse Reactions

8.1. Adverse Reaction Overview

SPORANOX has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued, and liver function testing performed. Before consideration is given to reinstituting therapy, the risks and benefits of SPORANOX use should be reassessed (see 7. Warnings and Precautions, Hepatic/Biliary/Pancreatic).

The most frequently reported adverse experiences in association with the use of SPORANOX were of gastrointestinal origin, such as dyspepsia, nausea, vomiting, diarrhea, abdominal pain and constipation. Other adverse experiences reported very rarely (< 1/10000) include reversible increases in hepatic enzymes, hepatitis, menstrual disorder, dizziness and allergic reactions (such as pruritus, rash, urticaria and angioedema), peripheral neuropathy, Stevens-Johnson syndrome, alopecia, hypokalemia, edema, congestive heart failure and pulmonary edema.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Adverse experiences during short-term therapy with SPORANOX occurred in 7.8% of patients. During long-term therapy in patients, most of whom had underlying pathology and received multiple concomitant treatments, the incidence of adverse experiences was higher (20.6%). The most common adverse experiences (reported by at least 1% of patients) during short-term or long-term therapy with SPORANOX are presented in Table 5.

Table 5: Most common adverse experiences (≥1%) during long-term therapy with SPORANOX in comparison with short-term therapy

	Short-term Therapy	Long-term Therapy
Total number of patients	12889	916
Body System[1]/ Adverse Event	Incidence (%)	
Gastrointestinal[1]	4.4	9.1
Nausea	1.6	2.9
Dermatological[1]	0.8	4.5
Rash	<1.0	1.6
Pruritus	<1.0	1.3
Central Nervous System[1]	2.1	4.3
Headache	1.0	1.1
Respiratory System[1]	<1.0	3.9
Liver and Biliary System[1]	0.11	2.7
Miscellaneous[1]	0.7	5.6
Edema	<1.0	1.0

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

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

8.3. Less Common Clinical Trial Adverse Reactions

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

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

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

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

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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

8.5. Post-Market Adverse Reactions

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

Blood and lymphatic system disorders: granulocytopenia, leukopenia, neutropenia, thrombocytopenia

Immune system disorders: serum sickness, angioneurotic edema, anaphylactic, hypersensitivity, anaphylactoid and allergic reactions

Infections and infestations: upper respiratory tract infection

Metabolism and nutrition disorders: hyperglycemia, hypertriglyceridemia, hypokalemia, hypomagnesemia

Psychiatric disorders: confusional state

Nervous system disorders: peripheral neuropathy, paresthesia, hypoesthesia, headache, dizziness, tremor

Eye disorders: visual disturbances, including vision blurred and diplopia

Ear and labyrinth disorders: tinnitus, transient or permanent hearing loss

Endocrine disorders: Pseudoaldosteronism

Cardiac disorders: cardiac failure, congestive heart failure, left ventricular failure, tachycardia, bradycardia

Vascular disorders: hypotension

Respiratory, thoracic and mediastinal disorders: pulmonary edema, dyspnea, dysphonia

Gastrointestinal disorders: pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhea, constipation, dysgeusia, gastrointestinal disorder

Hepatobiliary disorders: serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes, hepatic failure, hyperbilirubinemia

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus, rash erythematous, hyperhidrosis

Investigations: blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood urea increased, gamma-glutamyltransferase increased, hepatic enzyme increased, urine analysis abnormal

Musculoskeletal and connective tissue disorders: myalgia, arthralgia

Renal and urinary disorders: pollakiuria, urinary incontinence, renal impairment

Reproductive system and breast disorders: menstrual disorders, erectile dysfunction

General disorders and administration site conditions: edema, pyrexia, generalized edema, face edema, chills

9. Drug Interactions

9.1. Serious Drug Interactions

- SPORANOX is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. Increased plasma concentrations of these drugs, caused by coadministration with itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. Coadministration of a number of CYP3A4 substrates is contraindicated with SPORANOX. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Drugs that are contraindicated with SPORANOX are listed below:
    - methadone, disopyramide, dronedarone, quinidine, ticagrelor, apixaban, rivaroxaban, isavuconazole, ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine, irinotecan, venetoclax (for chronic lymphocytic leukemia/small lymphocytic lymphoma patients during initiation/titration/ramp-up phase), lurasidone, pimozide, triazolam, asunaprevir (boosted), felodipine, ivabradine, ranolazine, eplerenone, domperidone, naloxegol, lomitapide, lovastatin, simvastatin, fesoterodine (in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment), solifenacin (in subjects with severe renal impairment or moderate to severe hepatic impairment), eletriptan, colchicine (in subjects with renal or hepatic impairment), eliglustat.

See 2. Contraindications, Table 1 ; 3. Serious Warnings and Precautions Box.

9.2. Drug Interactions Overview

Itraconazole is a drug with a high interaction potential. The various types of interaction and associated general recommendations are described below. In addition, Table 6 provides a listing example of drugs that may interact with itraconazole, organized per drug family for easy reference.

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of

itraconazole. Coadministration of itraconazole with moderate or potent CYP3A4 inducers may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be reduced. Coadministration with moderate or potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole, which may result in increased or prolonged pharmacologic effects of itraconazole.

Absorption of itraconazole from the capsule formulation is reduced in subjects with reduced gastric acidity. Drugs that reduce gastric acidity impair the absorption of itraconazole from itraconazole capsules. To counteract this effect, it is recommended to administer itraconazole capsules with an acidic beverage (such as non-diet cola) upon coadministration with drugs that reduce gastric acidity (see 7. Warnings and Precautions, Gastrointestinal).

Itraconazole and its major metabolite, hydroxy-itraconazole are potent CYP3A4 inhibitors. Itraconazole is an inhibitor of the drug transporters P-glycoprotein and breast cancer resistance protein (BCRP). Itraconazole can inhibit the metabolism of drugs metabolized by CYP3A4 and can inhibit the drug transport by P-glycoprotein and/or BCRP, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. For some drugs, coadministration with itraconazole may result in decreased plasma concentrations of the drug or of the active moiety of the drug. This may result in reduced efficacy of the drug.

Following cessation of medical treatment with itraconazole, plasma concentrations decrease below the detection limit within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors the plasma concentrations decline slower. This is particularly important for consideration when initiating therapy with drugs whose metabolism is affected by itraconazole.

The following general recommendations apply, unless stated differently in Table 6 The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).
Table 6.

- 'CONTRAINDICATED': Under no circumstances is the drug to be coadministered with itraconazole. This applies to:
    - CYP3A4 substrates for which increased plasma concentrations may increase or prolong therapeutic and/or adverse effects to such an extent that a potentially serious situation may occur (see 2. Contraindications).
- 'NOT RECOMMENDED': It is recommended that the use of the drug be avoided, unless the benefits outweigh the potentially increased risks. If coadministration cannot be avoided, clinical monitoring is recommended, and the dosage of itraconazole and/or the coadministered drug adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Moderate or potent CYP3A4 inducers: not recommended from 2 weeks before and during treatment with itraconazole
    - CYP3A4/P-gp/BCRP substrates for which increased or decreased plasma concentrations result in significant risk: not recommended during and up to 2 weeks after treatment with itraconazole.
- 'USE WITH CAUTION': Careful monitoring is recommended when the drug is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely and the dosage of itraconazole and/or the coadministered drug adapted

as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:

- Drugs that reduce gastric acidity (itraconazole capsules only)
- Moderate or potent inhibitors of CYP3A4
- CYP3A4/P-gp/BCRP substrates for which increased or decreased plasma concentrations result in a clinically relevant risk

The list of examples of interacting drugs in the table below is not comprehensive and therefore the label of each drug that is coadministered with itraconazole should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to coadministration.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6: Examples of drugs that may interact with SPORANOX

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Alpha Blockers		
Alfuzosin Silodosin Tamsulosin	Alfuzosin C_{max} (↑↑), AUC (↑↑)[2] Silodosin C_{max} (↑↑), AUC (↑↑)[2] Tamsulosin C_{max} (↑↑), AUC (↑↑)[2]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of alfuzosin/ silodosin/tamsulosin-related adverse reactions[4].
Analgesics		
Alfentanil Buprenorphine (IV and sublingual) Oxycodone Sufentanil	Alfentanil AUC (↑↑ to ↑↑↑↑)[2] Buprenorphine C_{max} (↑↑), AUC (↑↑)[2] Oxycodone C_{max} ↑, AUC ↑↑ Sufentanil conc increase (extent unknown)[2,3]	**USE WITH CAUTIO**N, monitor for adverse reactions related to the analgesic[4], dose reduction of alfentanil/buprenorphine/ oxycodone/sufentanil may be necessary.
Fentanyl	Fentanyl IV AUC (↑↑)[2] Fentanyl other form. conc increase (extent unknown)[2,3]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of fentanyl-related adverse reactions[4].
Methadone	(R)-methadone C_{max} (↑), AUC (↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of methadone-related adverse reactions, such as potentially life-threatening respiratory depression, QT prolongation and TdP.
Anti-arrhythmics		
Digoxin	Digoxin C_{max} ↑, AUC ↑	**USE WITH CAUTION**, monitor for digoxin adverse reactions, dose reduction of digoxin may be necessary[4].

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Disopyramide	Disopyramide conc increase (↑↑)[2,3]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of disopyramide-related adverse reactions, such as serious arrhythmias including TdP.
Dronedarone	Dronedarone C_{max} (↑↑↑), AUC (↑↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of dronedarone-related adverse reactions, such as QT prolongation and cardiovascular death.
Quinidine	Quinidine C_{max} ↑, AUC ↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of quinidine-related adverse reactions, such as QT prolongation, TdP, hypotension, confusion and delirium.
Antibacterials		
Ciprofloxacin Erythromycin	Itraconazole C_{max} ↑, AUC ↑	**USE WITH CAUTION**, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
Clarithromycin	Clarithromycin conc increase (extent unknown)[2,3] Itraconazole C_{max} ↑, AUC ↑;	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or clarithromycin[4], dose reduction of itraconazole and/or clarithromycin may be necessary.
Isoniazid Rifampicin	Isoniazid: itraconazole conc. (↓↓↓)[2,3] Rifampicin: itraconazole AUC ↓↓↓	**NOT RECOMMENDED** from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Rifabutin	Rifabutin conc. increase (extent unknown) [2,3] Itraconazole: C_{max} ↓↓, AUC ↓↓	**NOT RECOMMENDED** from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of rifabutin-related adverse reactions[4].
Anticoagulants and Antiplatelet Drugs		
Vorapaxar	Vorapaxar C_{max} (↑), AUC (↑)[2]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of vorapaxar-related adverse reactions[4].
Edoxaban	Edoxaban C_{max} (↑), AUC (↑)[2]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of edoxaban-related adverse reactions[4].

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
		If concomitant use cannot be avoided, dose reduction of edoxaban is recommended
Coumarins (e.g., warfarin) Cilostazol	Coumarins (e.g., warfarin) conc increase (extent unknown)[2,3] Cilostazol C_{max} (↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for coumarins/cilostazol adverse reactions, dose reduction of coumarins/cilostazol may be necessary[4].
Dabigatran	Dabigatran C_{max} (↑↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for dabigatran adverse reactions, dose reduction of dabigatran may be necessary[4].
Ticagrelor	Ticagrelor C_{max} (↑↑), AUC (↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ticagrelor-related adverse reactions, such as bleeding.
Apixaban Rivaroxaban	Apixaban C_{max} (↑), AUC (↑)[2] Rivaroxaban C_{max} (↑), AUC (↑ to ↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of apixaban/rivaroxaban-related adverse reactions[4].
Anticonvulsants		
Carbamazepine	Carbamazepine conc. (↑)[2,3] Itraconazole conc. (↓↓)[2,3]	**NOT RECOMMENDED** from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk for carbamazepine-related adverse reactions[4].
Phenobarbital Phenytoin	Phenobarbital: itraconazole conc. (↓↓↓)[2,3] Phenytoin: itraconazole AUC ↓↓↓	**NOT RECOMMENDED** from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Antidiabetics		
Repaglinide Saxagliptin	Repaglinide C_{max} ↑, AUC ↑ Saxagliptin C_{max} (↑↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for repaglinide/saxagliptin adverse reactions, dose reduction of repaglinide/saxagliptin may be necessary[4].
Antihelminthics, antifungals and antiprotozoals		
Quinine	Quinine C_{max} ↔, AUC ↑	**USE WITH CAUTION**, monitor for quinine adverse reactions[4]. Refer to the Product Monograph (PM) for specific actions to be taken**.**
Isavuconazole	Isavuconazole C_{max} (↔), AUC (↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
		itraconazole. Increased risk of isavuconazole-related adverse reactions, such as hepatic adverse reactions, hypersensitivity reactions, embryo-fetal toxicity and cardiac disorders, including QTc interval shortening.
Praziquantel	Praziquantel C_{max} (↑↑), AUC (↑)[2]	**USE WITH CAUTION**, monitor for praziquantel adverse reactions, dose reduction of praziquantel may be necessary[4].
Antihistamines		
Bilastine Ebastine Rupatadine	Bilastine C_{max} (↑↑), AUC (↑)[2] Ebastine C_{max} ↑↑, AUC ↑↑↑ Rupatadine conc increase (↑↑↑↑)[2,3]	**USE WITH CAUTION**, monitor for bilastine/ebastine/rupatadine adverse reactions[4], dose reduction of bilastine/ebastine/rupatadine may be necessary.
Antimigraine Drugs		
Eletriptan	Eletriptan C_{max} (↑↑), AUC (↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Coadministration of eletriptan with SPORANOX can elevate plasma eletriptan concentrations which could result in serious adverse events.
Ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine)	Ergot alkaloids conc increase (extent unknown)[2,3]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism.
Antineoplastics		

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Bortezomib Brentuximab vedotin Busulfan Erlotinib Gefitinib Imatinib Ixabepilone Nintedanib Pemigatinib Ponatinib Ruxolitinib Sonidegib Tretinoin (oral) Vandetanib	Bortezomib AUC (↑)[2] Brentuximab vedotin AUC (↑)[2] Busulfan C_{max} ↑, AUC ↑ Erlotinib C_{max} (↑↑), AUC (↑)[2] Gefitinib C_{max} ↑, AUC ↑ Imatinib C_{max} (↑), AUC (↑)[2] Ixabepilone C_{max} (↔), AUC (↑)[2] Nintedanib C_{max} (↑), AUC (↑)[2] Pemigatinib C_{max} ↑, AUC ↑ Ponatinib C_{max} (↑), AUC (↑)[2] Ruxolitinib C_{max} (↑), AUC (↑)[2] Sonidegib C_{max} (↑), AUC (↑↑)[2] Tretinoin C_{max} (↑), AUC (↑)[2] Vandetanib C_{max} ↔, AUC ↑	**USE WITH CAUTION**, monitor for adverse reactions related to the antineoplastic drug[4], dose reduction of the antineoplastic drug may be necessary.
Idelalisib	Idelalisib C_{max} (↑), AUC (↑)[2] Itraconazole serum conc. increase (extent unknown)[2,3]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or idelalisib[4], dose reduction of itraconazole and/or idelalisib may be necessary.
Axitinib Bosutinib Cabazitaxel Cabozantinib Ceritinib Cobimetinib Crizotinib Dabrafenib Dasatinib Docetaxel Entrectinib Glasdegib Ibrutinib Lapatinib Nilotinib Olaparib Pazopanib Sunitinib Talazoparib Trabectedin Trastuzumab emtansine Vinca alkaloids	Axitinib C_{max} (↑), AUC (↑↑)[2] Bosutinib C_{max} (↑↑↑), AUC (↑↑↑)[2] Cabazitaxel C_{max} (↔), AUC (↔)[2] Cabozantinib C_{max} (↔), AUC (↑)[2] Ceritinib C_{max} (↑), AUC (↑↑)[2] Cobimetinib C_{max} ↑↑, AUC ↑↑↑ Crizotinib C_{max} (↑), AUC (↑↑)[2] Dabrafenib AUC (↑)[2] Dasatinib C_{max} (↑↑), AUC (↑↑)[2] Docetaxel AUC (↔ to ↑↑)[2] Entrectinib C_{max} ↑, AUC ↑↑↑ Glasdegib C_{max} (↑), AUC (↑↑)[2] Ibrutinib C_{max} (↑↑↑↑), AUC (↑↑↑↑)[2] Lapatinib C_{max} (↑↑), AUC (↑↑)[2] Nilotinib C_{max} (↑), AUC (↑↑)[2] Olaparib C_{max} ↑, AUC ↑↑ Pazopanib C_{max} (↑), AUC (↑)[2] Sunitinib C_{max} (↑), AUC (↑)[2] Talazoparib C_{max} ↑, AUC ↑ Trabectedin C_{max} (↑), AUC (↑)[2] Trastuzumab emtasine conc. increase (extent unknown)[2,3] Vinca alkaloid conc. increase (extent unknown)[2,3]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the antineoplastic drug[4]. Additionally: For cabazitaxel, even though the change in pharmacokinetic parameters did not reach statistical significance in a low-dose drug interaction study with ketoconazole, a high variability in the results was observed. For entrectinib, refer to the Product Monograph for specific actions to be taken. For ibrutinib, refer to the Product Monograph for specific actions to be taken.
Regorafenib	Regorafenib AUC (↓↓ by estimation of active moiety)[2]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Regorafenib efficacy may be reduced.

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Irinotecan	Irinotecan and its active metabolite conc increase (extent unknown)[2,3]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of irinotecan-related adverse reactions, such as potentially life-threatening myelosuppression and diarrhea.
Venetoclax	Venetoclax C_{max} (↑↑↑), AUC (↑↑↑)[2]	**CONTRAINDICATED** for chronic lymphocytic leukemia/small lymphocytic lymphoma patients during dose initiation/titration/ramp-up phase of venetoclax. Otherwise, **NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole[4]
Antipsychotics, Anxiolytics and Hypnotics		
Alprazolam Aripiprazole Brotizolam Buspirone Haloperidol Midazolam (iv) Perospirone Quetiapine Ramelteon Risperidone Zopiclone	Alprazolam C_{max} ↔, AUC ↑↑ Aripiprazole C_{max} ↑, AUC ↑ Brotizolam C_{max} ↔, AUC ↑↑ Buspirone C_{max} ↑↑↑↑, AUC ↑↑↑↑ Haloperidol C_{max} ↑, AUC ↑ Midazolam (iv) conc increase ↑↑[3] Perospirone C_{max} ↑↑↑, AUC ↑↑↑ Quetiapine C_{max} (↑↑), AUC (↑↑↑)[2] Ramelteon C_{max} (↑), AUC (↑)[2] Risperidone conc increase ↑[3] Zopiclone C_{max} ↑, AUC ↑	**USE WITH CAUTION**, monitor for adverse reactions related to the antipsychotic, anxiolytic or hypnotic drug[4], dose reduction of these drugs may be necessary.
Lurasidone	Lurasidone C_{max} (↑↑↑), AUC (↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of lurasidone-related adverse reactions, such as hypotension, circulatory collapse, severe extrapyramidal symptoms, seizures.
Pimozide	Pimozide C_{max} (↑), AUC (↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of pimozide-related adverse reactions, such as cardiac arrhythmias, possibly associated with QT prolongation and TdP.
Triazolam	Triazolam C_{max} ↑ to ↑↑, AUC ↑↑ to ↑↑↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of triazolam-related adverse reactions, such as seizures, respiratory depression, angioedema, apnea and coma.

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Antivirals		
Asunaprevir (boosted)	Asunaprevir C_{max} (↑↑↑), AUC (↑↑↑)[2]	**CONTRAINDICATED,** refer to the PM of the antiviral drug for specific actions to be taken.
Tenofovir disoproxil fumarate (TDF)	Tenofovir conc increase (extent unknown)[2,3]	**USE WITH CAUTION**, however, refer to the PM of the antiviral drug for specific actions to be taken.
Cobicistat	Cobicistat conc increase (extent unknown)[2,3] Itraconazole conc increase (extent unknown)[2,3]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole, dose reduction of itraconazole may be necessary.
Daclatasvir	Daclatasvir C_{max} (↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for daclatasvir adverse reactions[4], dose reduction of daclatasvir may be necessary.
Darunavir (boosted) Fosamprenavir (ritonavir-boosted)	Ritonavir-boosted darunavir: itraconazole C_{max} (↑↑), AUC (↑↑)[2] Ritonavir-boosted fosamprenavir: itraconazole C_{max} (↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
Elvitegravir (boosted)	Elvitegravir C_{max} (↑), AUC (↑)[2] Itraconazole conc increase (extent unknown)[2,3]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or elvitegravir (ritonavir-boosted)[4]. Dose reduction of itraconazole may be necessary; refer to the elvitegravir PM for specific actions to be taken.
Efavirenz Nevirapine	Efavirenz: itraconazole C_{max} ↓, AUC ↓ Nevirapine: itraconazole C_{max} ↓, AUC ↓↓	**NOT RECOMMENDED** from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Elbasvir/Grazoprevir	Elbasvir C_{max} (↔), AUC (↑)[2] Grazoprevir C_{max} (↔), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for adverse reactions related to the co-administered drugs[4]. Refer to the elbasvir/grazoprevir PM for specific actions to be taken.
Glecaprevir/Pibrentasvir	Glecaprevir C_{max} (↑↑), AUC (↑↑ to ↑↑↑)[2] Pibrentasvir C_{max} (↔ to ↑), AUC (↔ to ↑↑)[2]	**USE WITH CAUTION,** monitor for adverse reactions related to the co-administered drugs[4]. Refer to the glecaprevir/pibrentasvir PM for specific actions to be taken.
Indinavir	Itraconazole conc. ↑[3] Indinavir C_{max} ↔, AUC ↑	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or indinavir[4]. Dose reduction of itraconazole and/or indinavir may be necessary.

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Maraviroc	Maraviroc C_{max} (↑↑), AUC (↑↑↑)[2]	**USE WITH CAUTION** monitor for adverse reactions[4]. Dose reduction of maraviroc may be necessary.
Ritonavir	Itraconazole C_{max} (↑), AUC (↑↑)[2] Ritonavir C_{max} (↔), AUC (↑)[2]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or ritonavir[4]. Dose reduction of itraconazole may be necessary; refer to the ritonavir PM for specific actions to be taken.
Saquinavir	Saquinavir (unboosted) C_{max} ↑↑, AUC ↑↑↑ Itraconazole (with boosted saquinavir) C_{max} (↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or saquinavir[4]. Dose reduction of itraconazole may be necessary; refer to the saquinavir PM for specific actions to be taken.
Beta Blockers		
Nadolol	Nadolol C_{max} ↑↑, AUC ↑↑	**USE WITH CAUTION**, monitor for nadolol adverse reactions[4]. Dose reduction of nadolol may be necessary.
Calcium Channel Blockers		
Diltiazem	Diltiazem & Itraconazole conc increase (extent unknown)[2,3]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or diltiazem[4]. Dose reduction of itraconazole and/or diltiazem may be necessary.
Felodipine	Felodipine C_{max} ↑↑↑, AUC ↑↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of dihydropyridine-related adverse reactions, such as hypotension and peripheral edema.
Other dihydropyridines Verapamil	Dihydropyridine conc increase (extent unknown)[2,3] Verapamil conc increase (extent unknown)[2,3]	**USE WITH CAUTION**, monitor for dihydropyridine/verapamil adverse reactions[4], dose reduction of dihydropyridine/verapamil may be necessary.
Cardiovascular Drugs		
Aliskiren Riociguat Sildenafil (pulmonary hypertension) Tadalafil (pulmonary hypertension)	Aliskiren C_{max} ↑↑↑, AUC ↑↑↑ Riociguat C_{max} (↑), AUC (↑↑)[2] Sildenafil/Tadalafil conc increase (extent unknown but effect may be greater than reported under Urologic Drugs)[2,3]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole[4]. Increased risk of adverse reactions related to the cardiovascular drug.
Bosentan Guanfacine	Bosentan C_{max} (↑↑), AUC (↑↑)[2] Guanfacine C_{max} (↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for bosentan/guanfacine adverse

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
		reactions[4]. Dose reduction of bosentan/guanfacine may be necessary.
Ivabradine	Ivabradine C_{max} (↑↑), AUC (↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ivabradine-related adverse reactions, such as atrial fibrillation, bradycardia, sinus arrest and heart block.
Ranolazine	Ranolazine C_{max} (↑↑), AUC (↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ranolazine-related adverse reactions, such as QT prolongation and renal failure.
Contraceptives[1]		
Dienogest Ulipristal	Dienogest C_{max} (↑), AUC (↑↑)[2] Ulipristal C_{max} (↑↑), AUC (↑↑↑)[2]	**USE WITH CAUTION**, monitor for contraceptive adverse reactions[4], refer to the dienogest/ulipristal PM for specific actions to be taken.
Diuretics		
Eplerenone	Eplerenone C_{max} (↑), AUC (↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of eplerenone-related adverse reactions, such as hyperkalemia and hypotension.
Gastrointestinal Drugs		
Aprepitant Loperamide Netupitant	Aprepitant AUC (↑↑↑)[2] Loperamide C_{max} ↑↑, AUC ↑↑ Netupitant C_{max} (↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for aprepitant/loperamide/netupitant adverse reactions[4]. Dose reduction of aprepitant/loperamide may be necessary. Refer to the netupitant Product Monograph for specific actions to be taken.
Domperidone	Domperidone C_{max} ↑↑, AUC ↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of domperidone-related adverse reactions, such as serious ventricular arrhythmias and sudden cardiac death.
Drugs that reduce gastric acidity	Itraconazole: C_{max} ↓↓, AUC ↓↓	**USE WITH CAUTION**, Drugs that reduce gastric acidity: e.g., acid neutralizing medicines such as

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
		aluminum hydroxide, or acid secretion suppressors such as H_2- receptor antagonists and proton pump inhibitors. When co-treatment with acid neutralizing medicines (e.g., aluminum hydroxide) these should be administered at least 2 hours before or 2 hours after the intake of SPORANOX. (See 7. Warnings and Precautions.)
Naloxegol	Naloxegol C_{max} (↑↑↑), AUC (↑↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of naloxegol-related adverse reactions, such as opioid withdrawal symptoms.
Saccharomyces boulardii	*S. boulardii* colonization decrease (extent unknown)	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. S. boulardii efficacy may be reduced.
Immunosuppressants		
Budesonide Ciclesonide Cyclosporine Dexamethasone Fluticasone Methylprednisolone Tacrolimus Temsirolimus	Budesonide (inhalation) C_{max} ↑, AUC ↑↑; Budesonide (other form) conc increase (extent unknown)[2,3] Ciclesonide (inhalation) C_{max} (↑↑), AUC (↑↑)[2] Cyclosporine (iv) conc increase ↔ to ↑[3] Cyclosporine (other form) conc increase (extent unknown)[2,3] Dexamethasone C_{max} ↔ (iv) ↑ (oral), AUC ↑↑ (iv, oral) Fluticasone (inhalation) conc increase ↑↑[3] Fluticasone (nasal) conc increase (↑)[2,3] Methylprednisolone (oral) C_{max} ↑ to ↑↑, AUC ↑↑ Methylprednisolone (iv) AUC ↑↑ Tacrolimus (iv) conc increase ↑[3] Tacrolimus (oral) C_{max} (↑↑), AUC (↑↑)[2] Temsirolimus (iv) C_{max} (↑↑), AUC (↑↑)[2]	**USE WITH CAUTION,** monitor for immunosuppressant adverse reactions[4]. Dose reduction of the immunosuppressant drug may be necessary.
Everolimus Sirolimus (rapamycin)	Everolimus C_{max} (↑↑), AUC (↑↑↑↑)[2] Sirolimus C_{max} (↑↑), AUC (↑↑↑↑)[2]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole[4]. Increased risk of

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
		everolimus/sirolimus-related adverse reactions.
Lipid Regulating Drugs		
Atorvastatin	Atorvastatin C_{max} ↔ to ↑↑, AUC ↑ to↑↑	**USE WITH CAUTION**, monitor for atorvastatin adverse reactions[4]. Dose reduction of atorvastatin may be necessary.
Lomitapide	Lomitapide C_{max} (↑↑↑↑), AUC (↑↑↑↑)[2]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of lomitapide-related adverse reactions, such as hepatotoxicity and severe gastrointestinal reactions.
Lovastatin Simvastatin	Lovastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑ Simvastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of lovastatin/ simvastatin-related adverse reactions, such as myopathy, rhabdomyolysis and liver enzyme abnormalities.
Nonsteroidal Anti-Inflammatory Drugs		
Meloxicam	Meloxicam C_{max} ↓↓, AUC ↓	**USE WITH CAUTION**, monitor for reduced efficacy of meloxicam. Dose adaption of meloxicam may be necessary.
Respiratory Drugs		
Salmeterol	Salmeterol C_{max} (↑), AUC (↑↑↑↑)[1]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of salmeterol-related adverse reactions[4].
SSRIs, Tricyclics and Related Antidepressants		
Reboxetine Venlafaxine	Reboxetine C_{max} (↔), AUC (↑)[2] Venlafaxine C_{max} (↑), AUC (↑)[2]	**USE WITH CAUTION**, monitor for reboxetine/venlafaxine adverse reactions[4]. Dose reduction of reboxetine/venlafaxine may be necessary.
Urologic Drugs		
Darifenacin Vardenafil	Darifenacin C_{max} (↑↑↑), AUC (↑↑↑ to ↑↑↑↑)[2] Vardenafil C_{max} (↑↑), AUC (↑↑↑↑)[2]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of darifenacin/vardenafil-related adverse reactions[4].

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Dutasteride Imidafenacin Oxybutynin Sildenafil (erectile dysfunction) Tadalafil (erectile dysfunction and benign prostatic hyperplasia) Tolterodine	Dutasteride conc increase (extent unknown)[2,3] Imidafenacin C_{max} ↑, AUC ↑ Oxybutynin conc increase ↑[3] Sildenafil C_{max} (↑↑), AUC (↑↑ to ↑↑↑↑)[2] Tadalafil C_{max} (↑), AUC (↑↑)[2] Tolterodine C_{max} (↑ to ↑↑), AUC (↑↑)[2] in poor metabolizers of CYP2D6	**USE WITH CAUTION**, monitor for urologic drug adverse reactions[4]. Dose reduction of the urologic drug may be necessary; refer to the dutasteride PM for specific actions to be taken. (For sildenafil and tadalafil, see also Cardiovascular Drugs, Miscellaneous Drugs and Other Substances in this table.)
Fesoterodine	Fesoterodine C_{max} (↑↑), AUC (↑↑)[2]	**CONTRAINDICATED** in patients with moderate to severe renal or hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of fesoterodine-related adverse reactions, such as severe anticholinergic effects. **USE WITH CAUTION** in other patients: monitor for fesoterodine adverse reactions[4], dose reduction of fesoterodine may be necessary.
Solifenacin	Solifenacin C_{max} (↑), AUC (↑↑)[2]	**CONTRAINDICATED** in patients with severe renal or moderate to severe hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of solifenacin-related adverse reactions, such as anticholinergic effects and QT prolongation. **USE WITH CAUTION** in other patients, monitor for solifenacin drug adverse reactions[4]. Dose reduction of solifenacin may be necessary.
Miscellaneous Drugs and Other Substances		
Alitretinoin (oral) Cabergoline Cannabinoids Cinacalcet	Alitretinoin C_{max} (↑), AUC (↑)[2] Cabergoline C_{max} (↑↑), AUC (↑↑)[2] Cannabinoids conc increase, extent unknown but likely (↑↑)[2] Cinacalcet C_{max} (↑↑), AUC (↑↑)[2]	**USE WITH CAUTION**, monitor for alitretinoin/ cabergoline/cannabinoids/cinacalcet drug adverse reactions. Dose reduction of alitretinoin/ cabergoline/cannabinoids/cinacalcet may be necessary[4].
Colchicine	Colchicine C_{max} (↑), AUC (↑↑)[2]	**CONTRAINDICATE**D in patients with renal or hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of colchicine-related adverse reactions, such as decreased cardiac output, cardiac arrhythmias, respiratory

Examples of medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
		distress and bone marrow depression. **NOT RECOMMENDED** in other patients, during and for 2 weeks after treatment with itraconazole. Increased risk of colchicine-related adverse reactions[4].
Eliglustat	CYP2D6 EMs: Eliglustat C_{max} (↑↑), AUC (↑↑)[2] Higher increases are expected in CYP2D6 IMs/PMs and upon coadministration with a CYP2D6 inhibitor.	**CONTRAINDICATED** in CYP2D6 EMs taking a strong or moderate CYP2D6 inhibitor / CYP2D6 IMs and PMs, during and for 2 weeks after treatment with itraconazole. Increased risk of eliglustat-related adverse reactions such as prolongation of the PR, QTc, and/or QRS cardiac interval, and cardiac arrhythmias. **USE WITH CAUTION** in CYP2D6 EMs, monitor for eliglustat adverse reactions[4]. Dose reduction of eliglustat may be necessary.
Ergot alkaloids	Ergot alkaloids conc increase (extent unknown)[2,3]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism. (see also Antimigraine Drugs in this table)
Galantamine	Galantamine C_{max} (↑), AUC (↑)[2]	**USE WITH CAUTION**, monitor for galantamine adverse reactions[4]. Dose reduction of galantamine may be necessary.
Ivacaftor	Ivacaftor C_{max} (↑↑), AUC (↑↑↑)[2]	**USE WITH CAUTION**, monitor for ivacaftor adverse reactions[4]. Dose reduction of ivacaftor may be necessary.
Lumacaftor/Ivacaftor	Ivacaftor C_{max} (↑↑), AUC (↑↑)[2] Lumacaftor C_{max} (↔), AUC (↔)[2] Itraconazole conc decrease, extent unknown but likely ↓↓↓	**NOT RECOMMENDED** from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of ivacaftor-related adverse reactions[4].
Vasopressin Receptor Antagonists		
Conivaptan Tolvaptan	Conivaptan C_{max} (↑↑), AUC (↑↑↑↑)[2] Tolvaptan C_{max} (↑↑), AUC (↑↑↑)[2]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of conivaptan/tolvaptan-related adverse reactions[4].
Mozavaptan	Mozavaptan C_{max} ↑, AUC ↑↑	**USE WITH CAUTION**, monitor for mozavaptan adverse reactions[4]. Dose reduction of mozavaptan may be necessary.

1. CYP3A4 inhibitors (including itraconazole) may increase systemic contraceptive hormone concentrations. EMs: extensive metabolizers; IMs: intermediate metabolizers, PMs: poor metabolizers; TdP: Torsade de Pointes
   Note:
   Average increase:
   ↑: <100% (i.e. <2-fold);
   ↑↑: 100-400% (i.e. ≥2-fold to <5-fold);
   ↑↑↑: 400-900% (i.e. ≥5-fold and <10-fold);
   ↑↑↑↑: ≥10-fold;
   Average decrease:
   ↓: <40%;
   ↓↓: 40-80%;
   ↓↓↓: >80%;
   No effect: ↔
   For the effect (middle column) the name of the parent drug is stated, even when the effect is related to the active moiety or the active metabolite of a prodrug.
2. For drugs with arrows between brackets, the assessment was based on the mechanism of interaction and clinical drug interaction information with ketoconazole or other strong CYP3A4 inhibitors and/or inhibitors of P-glycoprotein or BCRP, modelling techniques, case reports and/or *in vitro* data. For the other drugs listed, the assessment was based on clinical drug interaction information with itraconazole.
3. Pharmacokinetic parameters were not available.
4. Please consult the corresponding Product Monograph (PM) for information on drug-related adverse reactions

9.5. Drug-Food Interactions

For optimal absorption, SPORANOX should be taken immediately after a full meal (see 10.3. Pharmacokinetics).

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

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

10.2. Pharmacodynamics

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

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

In vivo

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

Long-term administration of itraconazole (up to 400 mg/day for up to a maximum of 2 years) indicated a slight decrease in plasma cholesterol in 67 patients who had a baseline cholesterol plasma level higher than 200 mg/dL.

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

There was no significant effect of itraconazole 100 or 200 mg taken daily for 35 days on the serum levels of 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol in 12 volunteers.

In volunteers receiving single or multiple doses of itraconazole for up to 30 days, no effect on serum levels of the following hormones were observed: basal plasma cortisol, testosterone, aldosterone, cortisol response to cosyntropin (ACTH) and plasma prolactin and response of plasma prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to an intravenous luteinizing hormone-releasing hormone (LHRH) challenge.

Plasma progesterone and estradiol levels measured once weekly (before, during and for 2 weeks after a 5-week administration period of itraconazole 200 mg/day) and saliva progesterone concentrations measured daily during the 5-week administration reflected a totally normal hormonal profile throughout the menstrual cycle.

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

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

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

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

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

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.

10.3. Pharmacokinetics

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

Table 7: Pharmacokinetic parameters for itraconazole

	50 mg (fed)	100 mg (fed)	100 mg (fasted)	200 mg (fed)
C_{max} (ng/mL)	45 ± 16	132 ± 67	38 ± 20	289 ± 100
T_{max} (hours)	3.2 ± 1.3	4.0 ± 1.1	3.3 ± 1.0	4.7 ± 1.4
$AUC_{0-\infty}$ (ng.h/mL)	567 ± 264	1899 ± 838	722 ± 289	5211 ± 2116

Values are means ± standard deviation

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

Values given in Table 8 represent data from a crossover pharmacokinetic study in which 27 healthy male volunteers each took a single 200 mg dose of SPORANOX with or without food.

Table 8: Crossover pharmacokinetic study of itraconazole in healthy male volunteers

	Itraconazole		Hydroxy-itraconazole	
	Fed	Fasted	Fed	Fasted
C_{max} (ng/mL)	239 ± 85	140 ± 65	397 ± 103	286 ± 101
T_{max} (hours)	4.5 ± 1.1	3.9 ± 1.0	5.1 ± 1.6	4.5 ± 1.1
$AUC_{0-\infty}$ (ng.h/mL)	3423 ± 1154	2094 ± 905	7978 ± 2648	5191 ± 2489

$t_{½}$ (hours)	21 ± 5	21 ± 7	12 ± 3	12 ± 3

Values are means ± standard deviation

Steady-state concentrations were reached within 15 days following oral doses of 50-400 mg daily. Values given in Table 9 are data at steady-state from a pharmacokinetic study in which 27 healthy male volunteers took 200 mg SPORANOX b.i.d. (with food) for 15 days.

Table 9: Steady-state pharmacokinetic study of itraconazole in healthy male volunteers

	Itraconazole	Hydroxy-itraconazole
C_{max} (ng/mL)	2282 ± 514	3488 ± 742
C_{min} (ng/mL)	1855 ± 535	3349 ± 761
T_{max} (hours)	4.6 ± 1.8	3.4 ± 3.4
$AUC_{0-\infty}$ (ng.h/mL)	22569 ± 5375	38572 ± 8450
$t_{½}$ (hours)	64 ± 32	56 ± 24

Values are means ± standard deviation

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

Absorption

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

The oral bioavailability of itraconazole capsules is maximal when the capsules are given immediately after a full meal.

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H_2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see 7. Warnings and Precautions, Gastrointestinal and 9. Drug Interactions). Absorption of itraconazole under fasted conditions in these subjects is increased when SPORANOX is administered with an acidic beverage (such as a non-diet cola). When SPORANOX was administered as a single 200-mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H_2-receptor antagonist, itraconazole absorption was comparable to that observed when SPORANOX was administered alone (see 9. Drug Interactions).

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given (see 7. Warnings and Precautions, General).

Distribution

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

Concentrations of itraconazole in whole blood are 60% of those in plasma. Uptake in keratinous tissues, especially the skin, is up to 5 times higher than in plasma, and elimination of itraconazole is related to epidermal regeneration. Therefore, therapeutic levels in the skin persist for 2 to 4 weeks after discontinuation of a 4-week treatment. Therapeutic levels of

itraconazole in nails persist for 6 to 9 months after cessation of treatment. Itraconazole is also present in sebum and to a lesser extent in sweat. Itraconazole is extensively distributed into tissues which are prone to fungal invasion. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be 2 to 3 times higher than the corresponding plasma concentration and the uptake into keratinous tissues, skin in particular, up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma.

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

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

Special populations and conditions

- **Pediatrics:** No pharmacokinetic data are available in pediatric patients (see 7.1.3. Pediatrics).

- **Geriatrics:** See 7.1.4. Geriatrics.

- **Hepatic Insufficiency:** Itraconazole is predominantly metabolized in the liver. Pharmacokinetic data for patients with hepatic insufficiency is limited to subjects who received a single 100 mg dose of SPORANOX. A pharmacokinetic study using a single 100 mg dose of itraconazole (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. A statistically significant reduction in mean C_{max} (47%; mean cirrhotic C_{max} 87 ± 18 ng/mL, mean healthy C_{max} 164 ± 34 ng/mL) and a two-fold increase in the elimination half-life (37 ± 7 hrs and 16 ± 5 hrs, respectively) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC was similar in cirrhotic patients and in healthy subjects (mean cirrhotic AUC 1449 ± 207 ng.h/mL, mean healthy AUC 1856 ± 388 ng.h/mL). Data are not available in cirrhotic patients during long-term use of itraconazole. Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in cirrhotic patients should be considered when deciding to initiate therapy with other medicines metabolized by CYP3A4 (see 7. 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 7. Warnings and Precautions, Renal). Pharmacokinetic data in renally impaired patients is limited to subjects who received a single 200 mg dose of

SPORANOX. A pharmacokinetic study using a single 200 mg dose of itraconazole (four 50 mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; continuous ambulatory peritoneal dialysis: n=5). Mean ± SD pharmacokinetic parameters are summarized below.

Table 10: Mean pharmacokinetic parameters in renally impaired patients receiving a single 200 mg oral dose of itraconazole

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

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

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole (see 7. Warnings and Precautions, Renal and 4. Dosage and Administration, Patients with Renal Impairment).

11. Storage, Stability, and Disposal

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

Part 2: Scientific Information

13. Pharmaceutical Information

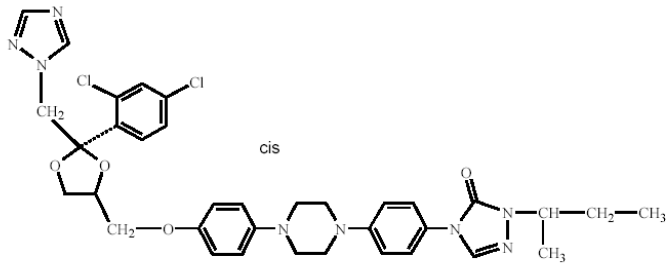
Drug Substance

Non-proprietary name of the drug substance: Itraconazole

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

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

Structural formula:



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

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

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

14. Clinical Trials

14.1. Clinical Trials by Indication

The clinical trial data on which the original indication was authorized is not available because this information cannot be accessed.

15. Microbiology

Itraconazole is an orally active triazole antifungal drug which demonstrates antifungal activity on a wide variety of fungi and yeast in vitro.

Itraconazole exhibits in vitro activity against *Aspergillus* spp., *Blastomyces dermatitidis*, *Cladosporium* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Geotrichum* spp., *Histoplasma* spp., including H. *capsulatum*, *Paracoccidioides brasiliensis*,*Talaromyces*

marneffei, *Sporothrix schenckii* and *Trichosporon*, *Epidermophyton floccosum*, *Fonsecaea* spp., *Malassezia* spp., *Microsporum* spp., *Pseudallescheria boydii* and *Trichophyton* spp.
MIC_{90}'s for the majority of medically important fungi are between 0.1 and 1.0 µg/mL, while fungicidal activity is obtained at higher concentrations (10 µg/mL). The in vitro activity of hydroxy-itraconazole (the only active metabolite) is comparable to the in vitro activity of itraconazole.

In vitro results vary considerably depending on culture medium, inoculum size, conditions of incubation, etc. Because of this variability of in vitro results, most fungi show a higher apparent sensitivity to itraconazole in vivo.

The principal fungus types that are not inhibited by itraconazole 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 guilliermondii* are generally the least susceptible *Candida* species, with some isolates showing unequivocal resistance to itraconazole in vitro.

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

Table 11: In vivo activity oral itraconazole

Infection	Animal	Delay/ duration [1] (days)	% of animals responding at dosage indicated (mg/kg/day)								Response
			1.25	2.5	5	10	20	40	80	160	
Candidiasis	Guinea pig	0/14	27		96						Negative kidney culture
	Rat	0/3		100							Survived 21 days
	Rabbit	+1/7							86[2]		Negative kidney culture
Aspergillosis	Guinea pig	0/14			83	75					Survived 28 days
	Guinea pig	+0/14			50	83					Survived 28 days
	IC[4] guinea pig	0/28			100						Survived 28 days
	IC[4] guinea pig	+1/28			80						Survived 28 days
	Mouse	0/5							47		Negative kidney culture
	Rabbit[3]	+3/14			100						Cured
Cryptococcosis	Guinea pig	+3/35				88	100				Negative culture (CSF excluded)
	Mouse	0/14								53	Negative CSF culture
	Rabbit	+4/14							73[2]		Negative CSF culture
Sporotrichosis	Guinea pig	0/28					80	100			Cured
Histoplasmosis	Guinea pig	0/14				63		100			Cured

Coccidioidomy-cosis	Rat Rat	- 3/14 +7/14					100[5] 80[5]				Negative lung culture Negative lung culture
Paracoccidioid-omycosis	Mouse	0/28				100					Survived 28 days

1. Delay in start of treatment relative to time of infection/duration of treatment.
2. 200 mg given to each animal, roughly equivalent to 80 mg/kg/day.
3. Itraconazole administered intravenously.
4. IC = immunocompromised by cyclophosphamide, corticosteroids or mechlorethamine.
5. Actual dosage 16 mg/kg/day.

Resistance and Cross-Resistance

Isolates from several fungal species, (including *Aspergillus fumigatus*), with decreased susceptibility to itraconazole have been isolated in vitro and from patients receiving prolonged therapy. Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14α-demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux.
Cross-resistance between members of the azole class has been observed within Candida spp., the finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed.

16. Non-Clinical Toxicology

General toxicology

Acute

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

Table 12: LD_{50} values for itraconazole 14 days after administration

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

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

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

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

Necropsy revealed no consistent drug-related macroscopic changes.

Long-term toxicity

Rats: 3 months

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

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

Rats: 3 months + 1 month recovery

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

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

Beagle dogs: 3 months

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

Beagle Dogs: 3 months + 1 month recovery

Itraconazole was also administered daily, via gelatin capsules, for 3 months to groups of 4 female and 4 male dogs at dose levels of 5, 20 or 80 mg/kg body weight/day. This study included both untreated control dogs and control dogs which received the vehicle (PEG 400) only. At the end of the dosage period, dogs from all groups were sacrificed for pathological examinations. Four other dogs (2 male and 2 female) from the untreated control groups, and the group receiving 80 mg/kg (high dose level) remained under observation for one additional month during which no compound or vehicle was administered (recovery period).

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

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

Rats: 6 months

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

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

Rats: 12 months

Itraconazole was administered to groups of 20 male and 20 female rats via the diet at dosage levels of 5, 20 and 80 mg/100 g food or approximately 5, 20 and 80 mg/kg/day (calculated mean compound intake of 3, 12 and 59 mg/kg/day in the males and 4, 27 and 131 mg/kg/day in the females). Drug-related overactivity and food wastage were observed in the rats receiving 20 or

80 mg/100 g food. The food consumption was estimated to have been decreased in the males of the 80 mg/100 g food group and the females of the 20 and 80 mg/100 g food groups. The food wastage biased the calculated compound intake in these groups.

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

Dogs: 12 months

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

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

Carcinogenicity

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

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

In rats, the doses were 3.2, 13.4 and 25.5 mg/kg body weight/day for the males and 4.7, 22.5, and 52.4 mg/kg body weight/day for the females. Pathological examination revealed, at the high dose and to a lesser extent at the mid dose, modifications of several organs such as abdominal mesothelia, adrenal, lung, lymph node, mammary gland, female genital tract, pituitary gland, skin with subcutis, thymus and urinary bladder. Male rats treated with the high dose of

25.5 mg/kg body weight/day (3.1x Maximum Recommended Human Dose [MRHD]) had a decrease in body weight gain and slight increase in the incidence of soft tissue sarcoma. These sarcomas may have been a consequence of chronic inflammatory reaction of the connective tissue related to a rat-specific response of hypercholesterolemia which was not observed in dogs or humans. In female rats, there was a slight decrease in body weight gain at the low-dose group and an increased wastage of food at the mid- and high-dose groups. Some altered blood parameters and a slight increase in mortality were observed in the high-dose group. Female rats treated with approximately 50 mg/kg body weight/day (6.25x MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) when compared to the control group. Although the occurrence of squamous cell carcinoma in the lung is extremely rare in untreated rats, the increased incidence in this study was not statistically significant.

Genotoxicity
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.

Reproductive and developmental toxicology
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 indicates 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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]SPORANOX®

Itraconazole capsules

This patient medication information is written for the person who will be taking **SPORANOX**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **SPORANOX**, talk to a healthcare professional.

Serious warnings and precautions box

- **Heart Problems:** You should not take SPORANOX if you have or have had heart problems like congestive heart failure. Signs or symptoms of congestive heart failure may be seen with use of SPORANOX. Stop taking SPORANOX and contact your healthcare professional right away if you have signs or symptoms of congestive heart failure (see **Serious side effects and what to do about them** table).
- **Drug Interactions:** Some medicines should NOT be taken during treatment with SPORANOX (see **Serious Drug Interactions** box and **The following may also interact with SPORANOX** sections).
- **Liver Problems:** SPORANOX in rare cases may cause liver toxicity, liver failure and death. Stop taking SPORANOX and contact your healthcare professional right away if you have signs or symptoms of liver problems (see **Serious side effects and what to do about them** table).

What SPORANOX is used for:

- SPORANOX is a medicine used to treat fungal infections of the skin, mouth, eyes, nails or internal organs.

How SPORANOX works:

SPORANOX goes into your bloodstream and travels to the site of the infection and kills the fungus causing your disease.

Recovery time depends on disease type and severity. For fungal nail infections, improvements may not be seen until several months after the treatment period has finished.

The ingredients in SPORANOX are:

Medicinal ingredients: itraconazole

Non-medicinal ingredients: D&C Red No.22 (eosine), D&C Red No.28 (phloxine B), FD&C Blue No.1 (brilliant blue), FD&C Blue No.2 (indigotin), gelatin, hypromellose, macrogol and sugar spheres (composed of maize starch, purified water and sucrose), and titanium dioxide.

SPORANOX comes in the following dosage forms:

- Capsule (pink and blue), with each capsule containing 100 mg of itraconazole

Do not use SPORANOX if:

- you have or have had congestive heart failure. SPORANOX could make it worse.
    - If you have congestive heart failure and you are being treated for a fungal infection of the skin or nails, you should not take SPORANOX.
    - If you are being treated for another kind of fungal infection and your healthcare professional decides that you need SPORANOX, be sure to get immediate medical help if you experience signs of heart failure (see **Possible side effects from using SPORANOX?**).
- you are taking certain medicines that must not be taken with SPORANOX (see **The following may interact with SPORANOX** section).
- you have ever had an allergic reaction to itraconazole or any of the other ingredients in SPORANOX (see **The ingredients in SPORANOX are?**).
- you have ever had an allergic reaction to other medicines you have taken to treat a fungal infection.
- you have a fungal infection of the skin or nails and are pregnant or planning to become pregnant.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SPORANOX. Talk about any health conditions or problems you may have, including if you:

- have kidney problems.
- have low white blood cell count, AIDS, or are an organ transplant patient.
- have a lung problem, including cystic fibrosis.
- have reduced stomach acidity. This may be due to a condition that affects your ability to produce stomach acids (such as achlorhydria) or if you are taking other medications that lowers stomach acidity.

Other warnings you should know about:

- **Driving and Using Machines:**
  SPORANOX can cause dizziness, blurred or double vision, or hearing loss. If you have these symptoms, do not drive or use machines.

- **Children and Adolescents (under 18 years of age):**
  SPORANOX is not recommended for use in children. There is limited information on the use of SPORANOX in children.

- **Pregnancy**
    - Do not take SPORANOX if you are pregnant or are planning to become pregnant. It may harm your unborn baby.

- If you are pregnant and your healthcare professional decides you need urgent treatment with SPORANOX, they will discuss with you the possible risks of taking this medicine during pregnancy.
- Serious birth defects have been seen in animals and women treated with SPORANOX during pregnancy. It is not known whether SPORANOX caused these defects.
- If you are taking SPORANOX, do not plan to become pregnant within 2 months of finishing your treatment.
- If you are able to become pregnant and are taking SPORANOX for the treatment of fungal skin or nail infections:
    - You must always use a reliable form of barrier birth control along with other methods of birth control (such as oral birth control pills or other hormonal methods like implants, injections).
    - You should also continue using a reliable form of birth control for 2 months after stopping treatment with SPORANOX. SPORANOX may remain in your blood for a time after therapy is stopped.

- **Breastfeeding**
    - Do not take SPORANOX if you are breast-feeding. SPORANOX passes into your breastmilk and may harm your baby.
    - Talk to your healthcare professional about the best way to feed your baby during treatment with SPORANOX.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

The following list of medicines must NOT be taken during your SPORANOX treatment:

<u>DO NOT take SPORANOX if you are taking any of the following medicines:</u>

- boosted asunaprevir, used in the treatment of Hepatitis C Virus
- eplerenone, felodipine, ivabradine, ranolazine, used to treat angina (crushing chest pain) or high blood pressure
- ticagrelor, apixaban, rivaroxaban, used to slow down blood clotting
- lomitapide, lovastatin, simvastatin, used to lower cholesterol
- triazolam, used to treat insomnia
- lurasidone, pimozide, used for psychotic disorders
- methadone, used for severe pain or to manage addiction
- dihydroergotamine or ergotamine (called ergot alkaloids), used in the treatment of migraine headaches
- ergometrine (ergonovine) (called ergot alkaloids), used to control bleeding and maintain uterine contraction after child birth
- eletriptan, used to treat migraine headaches
- irinotecan, used to treat cancer
- disopyramide, dronedarone, quinidine, used to treat irregular heart beat rhythms
- domperidone, used to treat nausea and vomiting
- isavuconazole, used to treat fungal infections
- naloxegol, used to treat constipation caused by taking opioid painkillers
- eliglustat, used to treat Gaucher disease type 1 (GD1)

If you have kidney or liver problems, DO NOT take SPORANOX while taking any of the following medicines:

- colchicine, used to treat gout
- fesoterodine or solifenacin when used to control irritated urinary bladder

Medicines that must NEVER be taken while you are on SPORANOX, if you have chronic lymphocytic leukemia/small lymphocytic lymphoma and you want to newly start this medicine or are making dose adjustments:

- venetoclax

Wait at least 2 weeks after stopping SPORANOX before taking any of these medicines.

Some medicines must not be taken at the same time, and if certain medicines are taken at the same time, changes need to be made (to the dose, for example).

The following may also interact with SPORANOX:

Medicines that can decrease the action of SPORANOX and are NOT recommended unless your healthcare professional feels it is necessary:

- carbamazepine, phenobarbital, phenytoin, used to treat epilepsy
- isoniazid, rifabutin, rifampicin, used to treat tuberculosis
- efavirenz, nevirapine, used to treat HIV/AIDS

Always tell your healthcare professional if you are using any of these medicines so that the appropriate precautions can be taken.

Wait at least 2 weeks after stopping these medicines before taking SPORANOX.

Medicines NOT recommended unless your healthcare professional feels it is necessary:

- axitinib, bosutinib, cabazitaxel, cabozantinib, ceritinib, cobimetinib, crizotinib, dabrafenib, dasatinib, docetaxel, entrectinib, glasdegib, ibrutinib, lapatinib, nilotinib, olaparib, pazopanib, regorafenib, sunitinib, talazoparib, trabectedin, trastuzumab emtansine, vinca alkaloids, used to treat cancer
- riociguat, sildenafil, tadalafil, when used to treat pulmonary hypertension (increased blood pressure in the blood vessels in the lungs)
- everolimus, sirolimus, used to prevent rejection of a transplant
- conivaptan, tolvaptan, used to treat low blood sodium
- edoxaban, used to slow down blood clotting
- alfuzosin, silodosin, used to treat benign prostatic enlargement
- aliskiren, used to treat high blood pressure
- carbamazepine, used to treat epilepsy
- colchicine, used to treat gout
- darifenacin, used to treat urinary incontinence
- fentanyl, a strong medication used to treat pain
- vorapaxar, used to treat heart attacks or strokes
- salmeterol, used to improve breathing
- tamsulosin, used to treat male urinary incontinence

- vardenafil, used to treat erectile dysfunction
- *Saccharomyces boulardii*, used to treat diarrhea
- lumacaftor/ ivacaftor, used to treat Cystic Fibrosis.

Wait at least 2 weeks after stopping these medicines before taking SPORANOX.

Medicines NOT recommended while you are on SPORANOX, when you are on a stable dose of this medicine:
- venetoclax

Wait at least 2 weeks after stopping SPORANOX before starting this medicine unless your healthcare professional feels it is necessary.

Medicines that may require a dose change (for either SPORANOX or the other medicine):
- ciprofloxacin, clarithromycin, erythromycin, antibiotics, used to treat bacterial infections
- bosentan, digoxin, nadolol and certain calcium-channel blockers including verapamil, used to treat heart or blood vessel conditions
- guanfacine, used to treat Attention Deficit Hyperactivity Disorder
- diltiazem, used to treat high blood pressure
- cilostazol, coumarins (e.g., warfarin), dabigatran, used to slow down blood clotting
- budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, used for conditions such as inflammations, asthma, and allergies)
- cyclosporine, tacrolimus, temsirolimus, used to prevent rejection of a transplant
- cobicistat, boosted elvitegravir, tenofovir disoproxil fumarate (TDF), maraviroc, and protease inhibitors: indinavir, ritonavir, boosted darunavir, ritonavir-boosted fosamprenavir, saquinavir, used to treat HIV/AIDS
- dienogest, ulipristal, used as birth control
- daclatasvir, glecaprevir/pibrentasvir, elbasvir/grazoprevir, used to treat Hepatitis C Virus
- bortezomib, brentuximab vedotin, busulfan, erlotinib, gefitinib, idelalisib, imatinib, ixabepilone, nintedanib, pemigatinib, ponatinib, ruxolitinib, sonidegib, tretinoin (oral), vandetanib, used to treat cancer
- alprazolam, brotizolam, buspirone, midazolam IV, perospirone, ramelteon, used for anxiety or to help you sleep
- alfentanil, buprenorphine, oxycodone, sufentanil, strong medications used to treat pain
- repaglinide, saxagliptin, used to treat diabetes
- aripiprazole, haloperidol, quetiapine, risperidone, used to treat psychosis.
- zopiclone, used to treat insomnia
- aprepitant, netupitant, used to treat nausea and vomiting during cancer treatment
- loperamide, used to treat diarrhea
- fesoterodine, imidafenacin, oxybutynin, solifenacin, tolterodine, used to control irritated urinary bladder
- dutasteride, used to treat benign prostatic enlargement
- sildenafil, tadalafil, used to treat erectile dysfunction
- praziquantel, used to treat fluke and tapeworms
- bilastine, ebastine, rupatadine, used to treat allergy
- reboxetine, venlafaxine, used to treat depression and anxiety
- quinine, used to treat malaria
- atorvastatin, used to lower cholesterol
- meloxicam, used to treat joint inflammation and pain

- cinacalcet, used to treat an overactive parathyroid
- mozavaptan, used to treat low blood sodium
- alitretinoin (oral formulation), used to treat eczema
- cabergoline, used to treat Parkinsons Disease
- cannabinoids, used to treat nausea and vomiting, weight loss for patients with immune system problems and muscle spasms in patients with Multiple Sclerosis
- ivacaftor, used to treat Cystic Fibrosis
- galantamine, used to treat Alzheimer's disease

How to take SPORANOX:

- Take SPORANOX exactly as your healthcare professional tells you.
  Always take SPORANOX right after a full meal because it is better taken up by the body this way. Swallow the capsules whole with some water.
- If you are taking acid-neutralizing medicines (i.e., antacids), you should take these at least 1 hour before, or 2 hours after your SPORANOX. For the same reason, if you take medicines that stop the production of stomach acid, you should take your SPORANOX with a non-diet cola beverage.
- Do NOT switch to itraconazole oral solution without talking to your healthcare professional.

Usual dose:

- Your healthcare professional will decide the right SPORANOX dose for you, and the length of SPORANOX treatment. This may depend on the type of fungus and the place of your infection.
- Do not skip any doses. Be sure to finish all your SPORANOX as instructed by your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much SPORANOX, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

- If you missed a dose of SPORANOX, take it as soon as you remember. This will help to keep a constant amount of medication in your blood.
- But, if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time to make up for a forgotten dose.

Possible side effects from using SPORANOX?

These are not all the possible side effects you may have when taking SPORANOX. If you experience any side effects not listed here, tell your healthcare professional.

- high triglyceride test results (fats in your blood)
- high liver test results
- nausea
- upset stomach
- vomiting

- abdominal pain
- constipation
- excess gas in the stomach
- diarrhea
- cough
- fluid in the lungs
- altered voice
- inflammation of the sinuses
- inflammation of the nose
- upper respiratory tract infection
- headache
- dizziness
- menstrual disorders
- erectile dysfunction
- confusion
- tremor
- sleepiness
- fatigue
- chills
- muscle weakness or pain
- painful joints
- chest pain
- generalized swelling
- unpleasant taste
- hair loss
- inflammation of the pancreas
- fever
- excessive sweating

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Blurry or Double Vision		✓	
Temporary or permanent Hearing loss			✓
Heart Problems: Develop shortness of breath, unusual swelling of feet, ankles or legs, sudden weight gain, unusually tired, cough up white or pink phlegm, begin to wake up at night, unusually fast or slow heartbeats		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Hypersensitivity(allergic reaction)**:** Skin rash**,** itching**,** hives**,** difficulty breathing or shortness of breath and/or, swelling of the face			✓
Liver Problems: Unusually tired**,** loss of appetite**,** nausea**,** abdominal pain**,** vomiting**,** yellow colour to skin or eyes**,** dark-coloured urine**,** pale stools			✓
Nerve Problems: Tingling, numbness, reduced sense of touch**,** weakness in the limbs**,** pain**,** pins and needles**,** prickling or burning.			✓
Photosensitivity (oversensitivity to sunlight)			✓
Severe Skin Disorder: Widespread rash with peeling skin and blisters in the mouth, eyes and genitals or rash with small pustules or blisters			✓
Tinnitus (Ringing in ears)		✓	
Urinary Incontinence (loss of ability to control urine or urinate much more than usual)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store SPORANOX capsules at room temperature (15°C to 30°C) in a dry place protected from light.
- Keep out of the reach and sight of children.

If you want more information about SPORANOX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website : innovativemedicine.jnj.com/canada; or by calling: 1-800-567-3331 or 1-800-387-8781

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