

# SPORANOX<sup>®</sup> Oral Solution

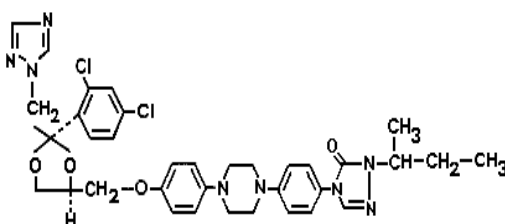
## PRODUCT INFORMATION

### NAME OF THE DRUG

Itraconazole

### DESCRIPTION

Itraconazole is a synthetic triazole antifungal agent. It has three chiral centres and is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs).



CAS-84625-61-6

C<sub>35</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>4</sub>

MW: 705.64

(±)-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.

It is a white to slightly yellowish powder, insoluble in water at pH 1-12, very slightly soluble in alcohols and freely soluble in dichloromethane.

SPORANOX oral solution contains itraconazole 10 mg/mL, hydroxypropyl-beta-cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour 1, cherry flavour 2, caramel flavour, saccharin sodium, sodium hydroxide and purified water.

### PHARMACOLOGY

*In vitro* studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

#### Pharmacokinetics

The oral bioavailability of SPORANOX oral solution is maximal when it is taken without food. During chronic administration, steady state is reached after 1-2 weeks. Peak plasma levels are observed 2 hours (fasting) to 5 hours (with food) following oral solution administration. After repeated administration of SPORANOX oral solution, at a dosage of 200 mg once a day in fasting condition, steady state plasma concentrations of itraconazole fluctuate between 1 and 2 micrograms/mL (trough to peak). When SPORANOX oral solution is taken with food, steady state plasma concentrations of itraconazole are about 25% lower.

The bioavailability of SPORANOX oral solution taken in a fasting condition is approximately 60% higher than the bioavailability of the capsule taken with a meal.

The bioavailability of SPORANOX oral solution in HIV patients is reduced by around 20% compared to normal volunteers. The bioavailability is not altered by the stage of infection. The recommended dosage has been shown to be effective in HIV patients.

The plasma protein binding of itraconazole is 99.8%. Concentrations of itraconazole in whole blood are 60% of those in plasma.

Itraconazole is extensively distributed into tissues, which are prone to fungal invasion but only minimally into CSF or ocular fluid. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than the corresponding plasma concentration.

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

After repeated oral administration, elimination of itraconazole from plasma is biphasic with a terminal half-life of 1.5 to 2 days. Faecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 35% of the dose is excreted as metabolites in the urine within 1 week.

### **Special population**

#### **Hepatic Impairment**

A pharmacokinetic study using a single 100mg dose of itraconazole (one 100mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC were seen between these two groups. A statistically significant reduction in mean  $C_{max}$  (47%) and a twofold increase in the elimination half-life ( $37 \pm 17$  hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. Patients with impaired hepatic functions should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in hepatic impairment patients ( $37.2 \pm 17$  h) should be considered when deciding to initiate therapy with other medications metabolised by CYP3A4. (See PRECAUTIONS: Drug Interactions.)

#### **Renal Impairment**

A pharmacokinetic study using a single 200mg dose of itraconazole (four 50mg capsules) was conducted in three groups of patients with renal impairment (uremic: n=7; hemodialysis: n=7, and continuous ambulatory peritoneal dialysis: n=5). In uremic / hemodialysis and continuous ambulatory peritoneal dialysis subjects,  $C_{max}$  were reduced compared with normal population parameters and listed below.

- $C_{max}$  132-417 (normal) / 50.9-505 ng.h/mL (uremic)
- $C_{max}$  18.2-341 (hemodialysis / 51.7-111 ng.h/mL (continuous ambulatory peritoneal dialysis)

Plasma concentration-versus-time profiles showed wide inter-subject variation in all three groups.

### **Microbiology**

#### **In vitro Susceptibility Tests, Dilution or diffusion techniques:**

Either quantitative (MIC) or breakpoint, should be used following a regulatory updated, recognised and standardised method (eg, Clinical and Laboratory Standard Institute [CLSI formerly NCCLS]). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

For itraconazole, breakpoints have only been established for *Candida* spp. from superficial mycotic infections (CLSI M27-A2, using laboratory controlled *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258). The proposed MIC breakpoints are as follows:

- Susceptible: A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antifungal compound in the blood reaches the concentrations usually achievable.
- Susceptibility that is "dose- or delivery-dependent" (S-DD): This category implies possible clinical applicability in body sites where the medicine is physiologically concentrated or in situations where high dosage of medicine can be used.

- Note that itraconazole MIC values for *Candida* species; *Cryptococcus neoformans*; *Blastomyces dermatidis*; *Coccidioides immitis*; *Histoplasma capsulatum*; and *Geotrichum* species were reported as  $\leq 1 \mu\text{g/mL}$ .
- Itraconazole MIC values for *Aspergillus flavus*, *Aspergillus fumigatus* *Trichosporon* species, *Fonsecaea pedrosoi*, and *Trichophyton* species were reported as  $\leq 1 \mu\text{g/mL}$ , although interpretive breakpoints have not been established for the filamentous fungi.
- Resistant: A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antifungal compound in the blood reaches the concentrations usually achievable; other therapy should be select.
  - *Candida krusei*, *Candida glabrata* and *Candida tropicalis* are generally the least susceptible *Candida* species, with some isolates showing unequivocal resistance to itraconazole *in vitro*.
  - The 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.
  - 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  $14\alpha$ -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., although resistance to one member of the class does not necessarily confer resistance to other azoles. Itraconazole-resistant strains of *Aspergillus fumigatus* have been reported.

#### Correlation between *in vitro* MIC results and clinical outcomes:

Susceptibility of a microorganism *in vitro* does not predict successful therapy. Host factors are often more important than susceptibility test results in determining clinical outcomes, and resistance *in vitro* should often predict therapeutic failure. Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

#### **Toxicology**

In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day. The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones and increased bone fragility. At a dosage level of 80 mg/kg/day over one year or 160 mg/kg/day for six months, itraconazole induced small tooth pulp with hypocellular appearance in some rats.

Increased relative adrenal weights and swollen adrenals (reversible) were seen in rats and dogs where plasma levels were comparable to those of human therapeutic doses. Adrenocortical function was not affected in studies in humans after the recommended daily doses; with higher doses (600 mg/day for 3 months), adrenal cortex response to ACTH stimulation was reduced in 1 of 8 patients, but returned to normal when the dosage was reduced.

## Clinical Trials

**Oral Candidiasis:** Two randomised, double-blind studies using fluconazole as a comparator were conducted in Group IV HIV-positive adults with culture proven oral candidiasis. In one study, itraconazole 100 mg b.i.d. (n = 135) was compared to fluconazole 100 mg o.d. (n = 132) each given for 7 days. Maintenance therapy of itraconazole 100 mg b.i.d. or fluconazole 100 mg o.d. one day per week was given for 12 weeks. At day 7, 86% of evaluable patients (n = 124) receiving itraconazole had a global evaluation of cured or markedly improved, 41% had a negative culture and 64% had a negative microscopic result. For evaluable patients receiving fluconazole (n = 112) the results were 87%, 32% and 49% respectively. The median time to relapse in the maintenance period using the Kaplan-Meier analysis of survival was greater than 108 and 94 days respectively. The global evaluation and time to relapse for itraconazole 100 mg b.i.d. and fluconazole 100 mg o.d. were equivalent. In the other double-blind study, itraconazole 100 mg b.i.d. (n = 68 evaluable patients) for 7 days was compared to itraconazole 100 mg b.i.d. (n = 68 evaluable patients) and fluconazole 100 mg o.d. (n = 78 evaluable patients) each for 14 days. A therapeutic response of 84%, 91% and 91% at day 15 was observed. The time to relapse and the relapse rate were similar. The mean symptom scores for soreness and burning, dysphagia, plaques, erythema and extent of lesions were almost identical.

**Oesophageal (with and without oral) Candidiasis:** Two randomised, double-blind, double-dummy studies comparing itraconazole oral solution with fluconazole in the treatment of oesophageal candidiasis with or without oral candidiasis were conducted. The first study compared itraconazole 100 mg b.i.d. (n = 58 evaluable patients) with fluconazole 50 mg for 7 days (n = 55 evaluable patients) in patients with AIDS. Pulse therapy of either itraconazole 100 mg b.i.d. or fluconazole 50 mg once weekly was continued for a further 12 weeks. In patients with oesophagitis a clinical response was seen in 93% of patients receiving itraconazole and 89% receiving fluconazole while in patients with oral candidiasis a clinical response was seen in 88% and 89% respectively. The median time to relapse was greater than 3 months by the Kaplan-Meier survival curve.

In the other study, 126 immunocompromised patients (92% HIV positive) with endoscopy-confirmed oesophageal candidiasis and a positive fungal culture were treated with either 100 mg itraconazole or fluconazole for 7 days after which treatment could be increased to 200 mg. Patients continued treatment for 2 weeks following resolution of symptoms and were then followed for a further 4 weeks. Clinical response was seen in 94% of 53 evaluable patients receiving itraconazole and 91% of 57 evaluable patients receiving fluconazole. Mycological cures were obtained in 92% evaluable itraconazole patients and 78% evaluable fluconazole patients. The median time to relapse was comparable for the 2 groups, around 26 days. In these two studies, itraconazole oral solution and fluconazole capsules were demonstrated to be equivalent in the treatment of oesophageal candidiasis.

**Oral and oesophageal candidiasis resistant to fluconazole:** Three open-label studies were conducted in patients with either oral or oesophageal candidiasis not responding to fluconazole. In the first study, 60 patients, of whom 40 were evaluable for efficacy, received itraconazole 100 mg b.i.d. for 14 days and 200 mg b.i.d. for a further 14 days if sufficient improvement had not occurred. A global assessment of cure at day 14 was seen in 60% of patients. Clinical cure at day 14 was 68% overall and 52% by intent to treat analysis. In the second study, 83 patients (65 evaluated for efficacy) received itraconazole 100 mg q.i.d. for 14 days. In patients who responded at 7 days the dose was reduced to itraconazole 200 mg for another 7 days. A maintenance phase of itraconazole 200 mg daily or 200 mg 3 times weekly was then continued for up to 6 months. Clinical response (cure or improved) at day 14 was 83% and 70% at study end point. Relapse occurred in 36% of patients at a mean time of 216 days. In the third study, adult HIV positive patients (n = 74) with oral candidiasis resistant to fluconazole received itraconazole 100 mg b.i.d. for 14 days and if not cured then treatment was continued for another 14 days. Follow up was for 6 weeks. Clinical improvement at the end of treatment was seen in 74% of evaluable patients and 70% by intent to treat analysis. The mean time to relapse was 13 days.

**Antifungal prophylaxis in neutropenia:** The prophylactic antifungal activity of itraconazole 5 mg/kg was studied in 3 main randomised trials on neutropenic patients with haematological malignancy. In the pivotal double-blind, placebo-controlled trial, patients received itraconazole 2.5 mg/kg b.i.d. (n = 201) or placebo (n = 204). Treatment was continued for a maximum of 8 weeks until neutrophil recovery or until another trial endpoint (e.g. deep fungal infections, superficial fungal infections, rescue IV amphotericin B) was reached. All patients also received both nystatin (500,000 IU q.i.d.) and ciprofloxacin (500 mg b.i.d.). Incidence of all fungal infections was significantly lower in the itraconazole group (23.9% vs 33.3%). Incidence of proven deep fungal infections including aspergillosis was 5 in the itraconazole group and 9 in the placebo group (p = 0.291, one-tailed analysis). There was no statistical difference between treatments in the use of IV amphotericin B as rescue medication.

The second double-blind, double-dummy trial compared itraconazole 2.5 mg/kg b.i.d. (n = 281) to oral amphotericin B 500 mg q.i.d. (n = 276). Treatment was continued for a maximum of 8 weeks until neutrophil recovery or until another trial endpoint was reached. There were no differences between itraconazole and amphotericin B treatments in the incidence of invasive aspergillosis or proven deep fungal infections. No difference between treatments was observed in the usage of rescue antifungal medications. The third open-label study compared itraconazole 2.5 mg/kg b.i.d. (n = 218, with 288 episodes of neutropenia) with fluconazole 100 mg o.d. (n = 227, with 293 episodes of neutropenia). Treatment was continued until neutrophil recovery or until another endpoint was reached. Although not statistically significant, 4 cases of aspergillosis (primary parameter) occurred in the fluconazole group compared to none in the itraconazole group. The number of breakthrough deep *Candida* infections was 2 and 1, and the number of breakthrough superficial infections was 4 and 11, for the itraconazole and the fluconazole groups, respectively.

## INDICATIONS

SPORANOX oral solution is indicated for:

- the treatment of oral and/or oesophageal candidiasis in HIV-positive or other immunocompromised patients.
- prophylaxis of fungal infections in neutropenic patients.

## CONTRAINDICATIONS

Co-administration of the following drugs is contraindicated with SPORANOX oral solution: terfenadine, astemizole, bepridil, nisoldipine, mizolastine, cisapride, dofetilide, levacetylmethadol (levomethadyl), quinidine, pimozide, sertindole, CYP3A4-metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam, triazolam and ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) (see **Interactions with other drugs**).

Serious cardiovascular adverse events, including death, ventricular tachycardia and torsades de pointes have been observed in patients taking itraconazole concomitantly with terfenadine, due to increased terfenadine concentrations induced by itraconazole.

Pharmacokinetic data indicates that another oral antifungal, ketoconazole, inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole, which may prolong QT intervals. *In vitro* data suggests that itraconazole, when compared to ketoconazole, has a less pronounced effect on the biotransformation system responsible for the metabolism of astemizole. Based on the chemical resemblance of itraconazole and ketoconazole, co-administration of astemizole with itraconazole is contraindicated.

Pharmacokinetic data indicates that oral ketoconazole potently inhibits the metabolism of cisapride resulting in an eight-fold increase in the mean AUC of cisapride. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. *In vitro* data suggest that itraconazole also markedly inhibits the biotransformation system mainly responsible for the metabolism of cisapride; therefore concomitant administration of itraconazole with cisapride is contraindicated.

Co-administration of itraconazole with oral midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects. These agents should not be used in patients treated with itraconazole. If midazolam is administered parenterally, special precaution is required since the sedative effects may be prolonged.

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

SPORANOX oral solution should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see **PRECAUTIONS**).

Itraconazole is contraindicated in pregnant women except for the treatment of life-threatening cases of systemic mycoses, where the potential benefits outweigh the potential harm to the foetus. Adequate contraceptive precautions should be taken by women of childbearing potential throughout itraconazole therapy, and continued until the next menstrual period following the completion of itraconazole therapy.

## **PRECAUTIONS**

### **Use with caution in the following circumstances**

#### **Peripheral neuropathy**

Isolated cases of peripheral neuropathy have also been reported, predominantly during long-term treatment with itraconazole. If neuropathy occurs that may be attributable to itraconazole, the treatment should be discontinued.

#### **Other azole antifungal agents**

There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX oral solution to patients with hypersensitivity to other azoles.

#### **Use in patients with congestive heart failure**

In a study with SPORANOX IV in healthy volunteers a transient asymptomatic decrease of the left ventricular ejection fraction, which resolved before the next infusion, was observed. The clinical relevance of these findings to the oral formulations is not known.

Itraconazole has been shown to have a negative inotropic effect. SPORANOX has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.

SPORANOX should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. The risk benefit assessment should consider factors such as the severity of the indication, the dosing regimen (e.g. total daily dose) and individual risk factors for congestive heart failure. Risk factors include cardiac disease, such as ischaemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other oedematous disorders. Patients with these risk factors, who are being treated with SPORANOX, should be informed of the signs and symptoms of congestive heart failure. Caution should be exercised and the patient monitored for the signs and symptoms of congestive heart failure. SPORANOX should be discontinued if such symptoms occur during treatment.

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 co-administering itraconazole and calcium channel blockers due to an increased risk of CHF.

### **Use in patients with cystic fibrosis**

Variability in therapeutic levels of itraconazole was observed and the therapeutic levels of itraconazole were not achieved in some patients. If a patient does not respond to SPORANOX oral solution, consideration should be given to switching to alternative therapy.

### **Treatment of severely neutropenic patients**

SPORANOX oral solution as treatment for oral and/or oesophageal candidiasis was not investigated in severely neutropenic patients. Due to the pharmacokinetic properties, SPORANOX oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis.

### **Hearing loss**

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see Contraindications and Interactions with other drugs). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

### **Use in patients with hepatic impairment**

Itraconazole is predominantly metabolised in the liver. Patient with impaired hepatic function should be carefully monitored when taking itraconazole and when deciding to initiate therapy with other medicationa metabolised by CYP3A4. Dose adjustments may be considered in these patients. (See Pharmacokinetics – special populations).

Patients with pre-existing abnormalities of hepatic function (raised liver enzymes, an active liver disease or patients who have experienced liver toxicity with other drugs) who require itraconazole should be monitored, regardless of the duration of therapy.

Rare cases of cholestatic jaundice and very rare cases of hepatitis have been reported. Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of SPORANOX. Most of these cases involved patients who had pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking other hepatotoxic drugs. Some patients had no obvious risk factors for liver disease. Some of these cases have been observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving SPORANOX treatment. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. In these patients treatment should be stopped immediately and liver function testing should be conducted.

In patients with raised liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases liver enzyme monitoring is necessary.

### **Use in patients with renal impairment**

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

### **Use in the elderly**

Clinical data on the use of SPORANOX oral solution in elderly patients is limited. Use SPORANOX oral solution in these patients only if the potential benefits outweigh the potential risks.

### **Use in children**

Since clinical data on the use of SPORANOX oral solution in paediatric patients is limited, its use in children is not recommended.

Limited safety experience is available with a dose of 5 mg/kg per day. The incidence of adverse events such as diarrhoea, abdominal pain, vomiting, fever, rash and mucositis was higher than in adults.

Toxicological studies have shown that itraconazole, when administered to rats, can produce bone toxicity. While such toxicity has not been reported in adult patients, the long-term effect of itraconazole in children is unknown (See **Toxicology**).

### **Carcinogenesis, mutagenicity, impairment of fertility**

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels of up to 80 mg/kg/day. Male rats treated with 25 mg/kg/day had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolaemia, which is a response of rats, but not dogs or humans to chronic itraconazole administration. Female rats treated with 50 mg/kg/day had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Itraconazole produced no mutagenic effects when assayed in appropriate bacterial, non-mammalian and mammalian test systems.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day even though parental toxicity was present at this dosage level.

Separate studies on the vehicle, hydroxypropyl-beta-cyclodextrin, have shown that this carrier molecule is not mutagenic. It did not have carcinogenic activity in mice at dietary dose levels up to 5 g/kg/day, but caused the development of pancreatic exocrine adenomas and adenocarcinomas in rats at dietary dose levels of 0.5 to 5 g/kg/day. Pancreatic exocrine tumours in rats may be due to a non-genotoxic mechanism involving stimulation of cholecystokinin release as a result of complexation of bile salts by hydroxypropyl-beta-cyclodextrin in the intestinal lumen. However, there is only indirect evidence for this hypothesis and its relevance in humans is not known.

Hydroxypropyl-beta-cyclodextrin had no effect on fertility when administered to male and female rats at dietary doses up to 5 g/kg/day or IV doses up to 400 mg/kg/day.

### **Toxicology**

(See **PHARMACOLOGY – Toxicology** section).

### **Use in pregnancy**

Category B3

Teratogenic effects: Itraconazole was found to cause a dosage-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day and in mice at dosage levels of approximately 80 mg/kg/day. In rats, the teratogenicity consisted of major skeletal defects and in mice it consisted of encephaloceles and/or macroglossia.

SPORANOX oral solution is contraindicated in pregnancy except in life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see **CONTRAINDICATIONS**).

There is limited information on the use of SPORANOX 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 casual relationship with SPORANOX has not been established.

Epidemiological data on exposure to SPORANOX during the first trimester of pregnancy (mostly in patients receiving short-term treatment for vulvovaginal candidiasis) did not show an increased risk of malformations as compared to control subjects not exposed to any known teratogens.

Women of childbearing potential taking SPORANOX oral solution should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of SPORANOX therapy.

### **Use in lactation**

Based on the determination of itraconazole concentration in the breast milk of lactating mothers who received a single daily dose of 400 mg itraconazole (200 mg b.i.d.), it was calculated that the exposure in the infant to itraconazole would be around 450 times lower than in the mother. The expected benefits of SPORANOX therapy should therefore be weighed against the potential risk of breast-feeding. In case of doubt, the patient should not breast-feed.

### **Interactions with other drugs**

#### ***Other drugs that affect itraconazole***

##### *Demonstrated interactions*

Itraconazole is mainly metabolised through CYP3A4. Potent inhibitors of this enzyme increase the bioavailability of itraconazole. This has been demonstrated *in vivo* with clarithromycin, erythromycin and indinavir and *in vitro* with ritonavir.

Rifampicin, phenytoin, rifabutin and isoniazid: These enzyme inducing drugs significantly reduce the bioavailability and plasma concentrations of itraconazole to an extent that efficacy may be largely reduced. The combination of itraconazole with these potent enzyme inducers is not recommended.

##### *Theoretical potential interactions:*

Other enzyme inducing drugs capable of reducing the bioavailability of itraconazole include phenobarbital and carbamazepine. Similar effects on the efficacy of itraconazole, as demonstrated with other potent enzyme inducers, should be anticipated.

#### ***Effects of itraconazole on other drugs***

Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family. This can result in an increase and/or a prolongation of their effects, including side effects. When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism. After stopping treatment, itraconazole plasma levels decline gradually, depending on the dose and duration of treatment (see **Pharmacokinetics**). This should be taken into consideration when other drugs are co-administered.

In addition to possible pharmacokinetic interactions involving the drug metabolising enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. Itraconazole can inhibit the metabolism of calcium channel blockers. Caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF.

##### *The following drugs are contraindicated with itraconazole:*

- Astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with SPORANOX oral solution since co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsade de pointes.
- CYP3A4 metabolized HMG-CoA reductase inhibitors such as lovastatin and simvastatin.
- Triazolam and oral midazolam.
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylethergometrine (methylethergonovine).
- Nisoldipine

Co-administration of terfenadine with itraconazole has led to elevated plasma concentrations of terfenadine, resulting in rare instances of life-threatening cardiac dysrhythmias and death.

The following drugs should be used with caution, and the plasma levels, effects or side effects of these drugs should be monitored. If co-administered with itraconazole, their dosage should be reduced if necessary:

- Midazolam I.V.: Special precaution is required since the sedative effect may be prolonged.
- Coumarin-like drugs (e.g. warfarin): It has been reported that itraconazole enhances the anticoagulant effect of coumarin-like drugs. Therefore, prothrombin time should be carefully monitored in patients receiving itraconazole and coumarin-like drugs simultaneously.
- HIV protease inhibitors such as indinavir, ritonavir and saquinavir. *In vitro* inhibition of the metabolism of saquinavir has been demonstrated. Inhibition of the metabolism of indinavir has been demonstrated *in vitro* and *in vivo*. The AUC of indinavir increased approximately 25% and  $C_{min}$  doubled when administered concomitantly with itraconazole (200 mg b.i.d.).
- Certain antineoplastic agents such as busulphan, docetaxel, trimetrexate and vinca alkaloids.
- CYP3A4 metabolised calcium channel blockers such as dihydropyridines (nifedipine, amlodipine besilate, felodipine and nimodipine) and verapamil. Oedema has been reported in patients concomitantly receiving SPORANOX and dihydropyridine calcium channel blockers. Patients should be monitored for adverse effects.
- Digoxin (via inhibition of P-glycoprotein): Co-administration of itraconazole and digoxin has led to increased plasma concentrations of digoxin. When digoxin is given concurrently with itraconazole, the physician is advised to monitor digoxin concentrations and reduce the dose as needed.
- Certain immunosuppressive agents - ciclosporin, sirolimus and tacrolimus. Co-administration of itraconazole and ciclosporin has led to increased plasma concentrations of ciclosporin. Although no studies have been conducted, literature cases suggest that the dose of ciclosporin should be reduced by 50% when itraconazole doses greater than 100mg daily are given. Ciclosporin concentrations should be monitored frequently and the dose adjusted accordingly.
- Certain CYP3A4 metabolised HMG-CoA reductase inhibitors such as atorvastin.
- Certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone.
- Norethisterone: The bioavailability of norethisterone has been shown to increase by 40% with concomitantly administered itraconazole.
- Buspirone: Co-administration of buspirone (10 mg/day) and itraconazole (200 mg/day) resulted in a marked increase in buspirone  $C_{max}$  (13 fold increase) and AUC (19 fold increase) accompanied by sedative effects and psychomotor impairment. If the drugs are used concomitantly, a low dose of buspirone (2.5 mg b.i.d.) is initially recommended with subsequent adjustment based on clinical assessment.
- Others: alfentanil, alprazolam, brotizolam, carbamazepine, cilostazol, disopyramide, ebastine, eletriptan, fentanyl, halofantrine, reboxetine, repaglinide and rifabutin.

#### *Theoretical potential interactions*

- Phenytoin: Although no studies have been conducted, concomitant administration of itraconazole and phenytoin may alter the metabolism of phenytoin; therefore, plasma concentrations of phenytoin should be monitored when it is given concurrently with itraconazole.
- Oral hypoglycaemic agents: Severe hypoglycaemia has been reported in patients concomitantly receiving azole fungal agents and oral hypoglycaemic agents. Blood glucose concentrations should be carefully monitored when itraconazole and oral hypoglycaemic agents are co-administered.

### *Potential interactions that have been excluded*

*In vitro* studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide and sulfamethazine.

No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed. The results of a study in which eight HIV-infected patients were treated with zidovudine, 8±0.4 mg/kg/day, with or without itraconazole, 100 mg b.i.d. showed that the pharmacokinetics of zidovudine are not significantly affected during co-administration with itraconazole.

No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

Absorption from SPORANOX oral solution is not affected by co-administration of H<sub>2</sub>-antagonists, in contrast to the effect seen with SPORANOX capsules.

### **Instructions to the patient**

Patients should be instructed to take SPORANOX oral solution at least one hour before food. For the treatment of oral and/or oesophageal candidiasis the solution should be swished around the oral cavity (approximately 20 seconds) and swallowed. There should be no rinsing after swallowing.

Patients should be instructed to report any signs and symptoms that may suggest liver dysfunction so that the appropriate laboratory testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stool.

### **ADVERSE REACTIONS**

With the use of SPORANOX oral solution, the most frequently reported adverse reactions were of gastrointestinal origin, such as diarrhoea, nausea, abdominal pain and vomiting. Less frequently reported adverse experiences include headache, reversible increases in hepatic enzymes, dizziness and allergic reactions (such as pruritis, rash, urticaria and angio-oedema).

Adverse experiences reported in association with the use of SPORANOX 100 mg capsules:

#### Common (>1%)

Body as a whole	dizziness, headache
Liver	reversible increases in hepatic enzymes
Gastrointestinal	nausea, vomiting, diarrhoea, abdominal pain, constipation, dyspepsia

#### Rare (<0.1%)

Body as a whole	allergic reactions such as pruritus, rash, urticaria and angio-oedema
Endocrine	menstrual disorder

#### Very rare (<0.01%)

Liver	hepatitis (especially during prolonged treatment)
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### *Postmarketing experience*

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience with SPORANOX (all formulations) that meet threshold criteria are included in the table below. The adverse drug reactions are ranked by frequency, using the following convention: Very common (≥ 1/10); Common (≥1/100 and < 1/10); Uncommon (≥1/1,000 and < 1/100); Rare (≥1/10,000 and < 1/1000); Very rare (<1/10,000), including isolated reports.

The frequencies below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates of incidence that might be obtained in clinical or epidemiological studies.

Blood and Lymphatic System Disorders	Very rare: leucopenia and neutropenia, thrombocytopenia
Immune system disorders	Very rare: Serum sickness, angioneurotic oedema, anaphylactic, anaphylactoid and allergic reactions
Metabolism and Nutrition Disorders	Very rare: Hypertriglyceridemia, hypokalaemia
Nervous System Disorders	Very rare: Peripheral neuropathy, paraesthesia, hypoaesthesia, headache, dizziness
Eye Disorders	Very rare: Visual disturbances, including vision blurred and diplopia
Ear and Labyrinth Disorder	Very rare: Tinnitus, transient or permanent hearing loss
Cardiac Disorders	Very rare: Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders	Very rare: Pulmonary oedema
Gastrointestinal Disorders	Very rare: * <i>Pancreatitis</i> , abdominal pain, vomiting, dyspepsia, nausea, diarrhoea, constipation, dysgeusia
Hepato-biliary disorders	Very rare: Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes
Skin and Subcutaneous Tissue Disorders	Very rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus
Musculoskeletal and connective tissue disorders	Very rare: Myalgia, arthralgia
Renal and Urinary Disorders	Very rare: Pollakiuria, urinary incontinence
Reproductive System and Breast Disorders	Very rare: Menstrual disorders, erectile dysfunction
General Disorders and Administration Site Conditions	Very rare: Oedema, * <i>pyrexia</i>

## DOSAGE AND ADMINISTRATION

SPORANOX oral solution should be taken on an empty stomach at least 1 hour before food.

Treatment of oral and/or oesophageal candidiasis: 200 mg (2 measuring cups or 20 mL) once a day or 100 mg (1 measuring cup or 10 mL) twice a day for 1 week. If there is no response after 1 week, treatment should be continued for another week.

Treatment of fluconazole resistant oral and/or oesophageal candidiasis: 200 mg (2 measuring cups, 20 mL) daily in one or two intakes for 2 weeks. If there is no response after 2 weeks the dose should be increased to 400 mg/day for a further 2 weeks.

Prophylaxis of fungal infections: 5 mg/kg per day administered as a twice daily dose until recovery of neutrophils for up to 8 weeks.

Instructions for use: The bottle comes with a child-resistant cap and should be opened by pushing the plastic screw cap down whilst turning it counter clockwise.

## **OVERDOSAGE**

Itraconazole is not removed by dialysis. In the event of accidental overdosage, supportive measures should be employed. Contact the Poisons Information Centre on 131 126 for advice on management.

## **PRESENTATION**

SPORANOX 10 mg/mL oral solution (150 mL) is supplied in amber glass bottles with a child-resistant cap.

### **Storage**

Store below 25°C.

## **SPONSOR**

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\*Please note change(s) presented as *\*italicised text* in Product Information