
SPORANOX[®] Capsules

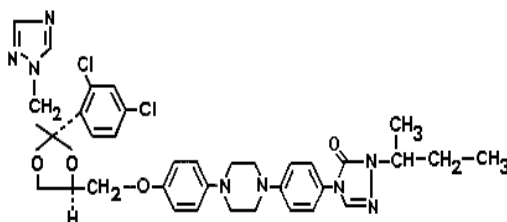
PRODUCT INFORMATION

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

C₃₅H₃₈Cl₂N₈O₄

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 alcohol and freely soluble in dichloromethane.

SPORANOX capsules contain itraconazole 100 mg, sucrose, starch, hypromellose and macrogol 20,000 in a hard gelatin capsule.

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 capsules is maximal and appears to be more consistent when they are taken immediately after a meal. However, there is a marked intersubject variability. The observed absolute oral bioavailability of itraconazole was 55%. If administered in the fasting state, C_{max} and AUC are about 30-40% lower than after a meal. Peak plasma levels are reached 3 to 5 hours following an oral dose. Elimination from plasma is biphasic with a terminal half-life of 1.5 to 2 days. During chronic administration, steady state is reached after 10-14 days. Mean steady state plasma concentrations of itraconazole 3-4 hours after drug intake are 0.4 microgram/mL (100 mg o.d.), 1.1 micrograms/mL (200 mg o.d.) and 2.0 micrograms/mL (200 mg b.i.d.).

The plasma protein binding of itraconazole is 99.8%. Concentrations of itraconazole in whole blood are 60% of those in plasma. Steady state itraconazole levels in the skin vary according to the distribution of sebaceous glands, ranging from one third of plasma levels in the skin of the palms to double plasma levels in the skin of the back. Itraconazole is eliminated from keratinous tissues by the shedding of cells during normal regeneration. Itraconazole is undetectable in the plasma within 7 days of stopping therapy, but levels at or above the MIC₉₀ for dermatophytes persist in the skin for one or two weeks after discontinuation of a 4-week treatment. Itraconazole is present at high concentrations in sebum but levels in sweat are negligible.

Itraconazole is extensively distributed into most tissues that 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 metabolised 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. Serum antifungal drug levels measured by bioassay were about 3 times those of itraconazole assayed by high performance liquid chromatograph. 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 a 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 ± 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 ± 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 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., 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

Histoplasmosis: In five open-label, non-comparative studies in patients (n = 136) with histoplasmosis exposed to treatment and maintenance therapy with itraconazole: sixty-one patients (45%) were HIV infected and 8 patients (6%) had other causes of immunosuppression. Ninety-eight patients (72%) had disseminated disease and 42 patients (31%) had other forms of histoplasmosis. Overall, 135 of the 136 patients (approx. 100%) responded. Five patients (4%) relapsed while on treatment. Efficacy was demonstrated for the oral treatment and maintenance therapy of histoplasmosis, both in immunocompromised and non-immunocompromised patients at the recommended dose of 200 - 400 mg/day for 8 months.

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

Intermittent (pulse) treatment of onychomycosis: *Onychomycosis of the toe nail:* In a double-blind study (n= 129 total) there was no significant difference in clinical and mycological success and overall response between itraconazole 200 mg b.i.d. one week per month (pulse) for 3 months and continuous treatment of itraconazole 200 mg o.d. for 3 months. In an open study (n = 50 total) there was no significant difference in clinical and mycological success and overall response between a 3 pulse and 4 pulse regimen.

Onychomycosis of the fingernail: In a double-blind, placebo controlled study (n = 71 total) a treatment of itraconazole 200 mg b.i.d. one week per month was more effective than placebo. The clinical and mycological success for itraconazole pulse treatment in compliant patients was 77% and 73% respectively and for placebo was nil and 12%. In an open study 84% of patients receiving 2 pulse treatments (n = 48) and 91% receiving 3 pulse treatments (n = 68) showed a clinical success and 77% and 85% respectively showed a mycological cure at endpoint.

Aspergillosis: In nine open-label studies of patients (n = 719) with systemic aspergillosis and treated with itraconazole, an overall response rate of 63% was observed. This varied according to the clinical syndrome, e.g. pulmonary aspergilloma (60%), bronchopulmonary (78%), invasive (62%) and extra-pulmonary (62%). In eight patients with cerebral aspergillosis the response rate was 13%. In a randomised, double-blind, comparator trial against amphotericin B in patients with proven or highly suspected aspergillosis, 6 of 8 patients receiving itraconazole responded and 2 of 5 patients responded on amphotericin B. The numbers are too small to assert any difference between treatments. The recommended dose for systemic aspergillosis is 200 mg/day for 2 - 5 months, with a dose of 200 mg twice daily for invasive or disseminated disease.

Sporotrichosis: In four open-label, non-comparative studies of patients (n = 124) with sporotrichosis, 115 of 124 patients (93%) treated with itraconazole demonstrated a complete or marked remission rate. The recommended dosage is 100 - 200 mg/day for 3 months. Treatment duration may be longer in patients with lymphatic/lymphocutaneous and extracutaneous sporotrichosis.

Candidiasis: In three open-label studies of patients (n = 143) with systemic candidiasis and treated with itraconazole, patients with urinary and pulmonary candidiasis responded with high efficacy, although the numbers with these conditions were small. An 85% response rate was observed in patients with oral and oesophageal candidiasis who had underlying cancer and were receiving chemotherapy and/or antibiotics or who had HIV/AIDS. In non-neutropenic patients with non-invasive candidiasis the response rate was 76%. The recommended dose is 100 - 200 mg/day for 3 weeks to 7 months.

INDICATIONS

SPORANOX is indicated for use in adults for the treatment of:

- Superficial dermatomycoses not responding to topical treatment.
- Fungal keratitis which has failed to respond to topical treatment or where the disease is either progressing rapidly or is immediately sight threatening.
- Pityriasis versicolor not responding to any other treatment.
- Vulvovaginal candidiasis not responding to topical treatment.
- Oral candidiasis in immunocompromised patients.
- Onychomycosis caused by dermatophytes.
- Systemic mycoses:
 - Systemic aspergillosis, histoplasmosis, sporotrichosis.
 - Treatment and maintenance therapy in AIDS patients with disseminated or chronic pulmonary histoplasmosis infection.
 - Treatment of oropharyngeal and/or oesophageal candidiasis when first line systemic antifungal therapy is inappropriate or has proven ineffective.
 - Treatment of non-invasive candidiasis in non-neutropenic patients when first-line systemic antifungal therapy is inappropriate or has proven ineffective. This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity.

CONTRAINDICATIONS

Co-administration of the following drugs is contraindicated with SPORANOX capsule: 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 co-administration 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 capsules are 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 capsules should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see **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 fetus. 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.

Decreased gastric acidity:

Absorption of itraconazole from SPORANOX capsules is impaired when the gastric acidity is decreased. In patients also receiving acid neutralising medicines (e.g. aluminium hydroxide), these should be administered at least 2 hours after the intake of itraconazole. In patients with achlorhydria, such as certain AIDS patients and patients on acid secretion suppressors (e.g. H₂-antagonists, proton-pump inhibitors), it is advisable to administer SPORANOX capsules with a cola beverage.

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 capsules 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 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.

Immunocompromised patients

In some immunocompromised patients (e.g. neutropenic, AIDS or organ transplant patients) the oral bioavailability of SPORANOX capsules may be decreased.

Patients with immediately life-threatening systemic fungal infections

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

Patients with AIDS

In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal and non-

meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

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 the elderly

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

Use in children

The efficacy and safety of itraconazole have not been established in children. Since clinical data on the use of itraconazole in children is limited, SPORANOX capsules should not be used in these patients unless the potential benefit outweighs the potential risks.

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**).

Carcinogenicity, 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.

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 capsules are 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 capsules 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, the plasma levels of itraconazole 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.

Demonstrated interactions

The following drugs are contraindicated with itraconazole:

- Astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozone, 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 methylergometrine (methylergonovine).
- 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, zidovudine and zalcitabine. *In vitro* inhibition of the metabolism of zidovudine has been demonstrated. Inhibition of the metabolism of indinavir has been demonstrated *in vitro* and *in vivo*. The AUC for indinavir increased approximately 25% and C_{min} doubled when administered concomitantly with itraconazole (200 mg b.i.d.).
- Certain antineoplastic agents such as busulfan, 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 dosage 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 case reports suggest that the dose of ciclosporin should be reduced by 50% when itraconazole doses greater than 100 mg daily are given. Ciclosporin concentrations should be monitored frequently and the dose adjusted accordingly.
- Certain CYP3A4 metabolised HMG-CoA reductase inhibitors such as atorvastatin.
- 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 marked increase in the C_{max} of buspirone (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 rufabutin.

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 AZT (zidovudine) and fluvastatin has been observed.

The results from a study in which eight HIV-infected individuals 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 concomitant administration of itraconazole.

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

Instructions to the patient

Patients should be instructed to take SPORANOX capsules with food.

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

In clinical studies involving short periods of treatment with itraconazole the overall incidence of adverse experiences is about 7%. In patients receiving prolonged (approximately 1 month) continuous treatment especially, the incidence of adverse experiences was higher (about 15%).

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.
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DOSAGE AND ADMINISTRATION

It is essential that SPORANOX capsules are taken immediately after a meal for maximal absorption. Treatment schedules are as follows:

Superficial dermatomycoses:

- Tinea corporis, tinea cruris: 1 capsule (100 mg) daily for 2 weeks.
- Tinea pedis, tinea manus: 1 capsule (100 mg) daily for 4 weeks.

Fungal keratitis:

- 2 capsules (200 mg) once daily for 3 weeks.

Pityriasis versicolor:

- 2 capsules (200 mg) once daily for 1 week

Vulvovaginal candidiasis:

- 2 capsules (200 mg) morning and evening for 1 day or 2 capsules (200 mg) once daily for 3 days.

Oral candidiasis in immunocompromised patients:

- 1 capsule (100 mg) or 2 capsules (200 mg) daily for 4 weeks.

Onychomycosis:

- 2 capsules (200 mg) once daily for 3 months.

OR

- Pulse therapy (see table below):

A pulse treatment consists of two capsules twice daily (200 mg b.i.d.) for one week. Two pulse treatments are recommended for fingernail infections, three pulse treatments for toenail infections. Pulse treatments are always separated by a 3-week drug-free interval. Clinical response will become evident as the nail regrows, following discontinuation of the treatment.

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	Pulse 1	Itraconazole free weeks			Pulse 2	Itraconazole free weeks			Pulse 3
Fingernails only	Pulse 1	Itraconazole free weeks			Pulse 2				

Systemic mycoses:

(Dosage recommendations vary according to the infection treated)

INDICATION	DOSE	USUAL DURATION	REMARKS
Aspergillosis	200 mg o.d.	2 - 5 months	Increase dose to 200 mg b.i.d. in cases of invasive or disseminated disease
Histoplasmosis	200 mg o.d. - 200 mg b.i.d.	8 months	Continue as necessary in AIDS patients. Maintenance therapy: 200 mg o.d.

Sporotrichosis	100 mg o.d.	3 months	Some patients may require 200 mg daily.
Candidiasis	100 - 200 mg o.d.	3 weeks - 7 months	-

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 is available as capsules containing 100 mg of itraconazole, with a blue opaque cap and pink transparent body. They are supplied in unit-dose blister packs.

Storage

Store below 25°C.

SPONSOR

JANSSEN-CILAG Pty Ltd
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*Please note change(s) presented as **italicised text* in Product Information