TRADE NAME OF THE MEDICINAL PRODUCT
SPORANOX CAPSULES

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 100 mg itraconazole in a pellet formulation.
For excipients, see 'List of Excipients'.

PHARMACEUTICAL FORM
Capsules for oral administration.

CLINICAL PARTICULARS
Therapeutic Indications
SPORANOX capsules are indicated for the treatment of the following conditions:

- Gynecological indications:
  - Vulvovaginal candidosis.
- Dermatological / mucosal / ophthalmological indications:
  - Dermatomycosis;
  - Pityriasis versicolor;
  - Oral candidosis;
  - Fungal keratitis.
- Onychomycosis, caused by dermatophytes and/or yeasts.
- Systemic mycoses
  - Systemic aspergillosis and candidosis;
  - Cryptococcosis (including cryptococcal meningitis): in immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system, SPORANOX is indicated only when first line treatment is considered inappropriate or has proven ineffective;
  - Histoplasmosis;
  - Blastomycosis;
  - Sporotrichosis;
  - Paracoccidioidomycosis;
  - Other rarely occurring systemic or tropical mycoses

Posology And Method Of Administration
For optimal absorption administer SPORANOX capsules immediately after a full meal.
The capsules must be swallowed whole.

Gynecological indication		
Indication	**Dose**	**Treatment Duration**
Vulvovaginal candidosis	200 mg b.i.d. or 200 mg once daily	1 day or 3 days
Dermatological / mucosal / ophthalmological indications		
Indication	**Dose**	**Treatment Duration**
Dermatomycosis	200 mg once daily or 100 mg once daily	7 days or 15 days
Highly keratinized regions as in plantar tinea pedis and palmar tinea manus	200 mg b.i.d. or	7 days or

	100 mg once daily	30 days
Pityriasis versicolor	200 mg once daily	7 days
Oral candidosis	100 mg once daily	15 days
In some immunocompromised patients (e.g. neutropenic, AIDS or organ transplant patients), the oral bioavailability of itraconazole from SPORANOX capsules may be decreased. Therefore the doses may need doubling.		
Fungal keratitis	200 mg once daily	21 days The duration of treatment should be adjusted to the clinical response.

Onychomycosis, caused by dermatophytes and/or yeasts

Onychomycosis **Pulse treatment**	**Dose and Treatment duration**
	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, and 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 re-grows, following discontinuation of the treatment.

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			

Onychomycosis **Continuous treatment**	**Dose**	**Treatment duration**
Toenails with or without fingernail involvement	200 mg once daily	3 months

Elimination of itraconazole from skin and nail tissue is slower than from plasma. Optimal clinical and mycological response is 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.

Systemic mycoses			
Indication	**Dose**	**Median Treatment Duration**[1]	**Remarks**
Aspergillosis	200 mg once daily	2-5 months	Increase dose to 200 mg b.i.d. in case of invasive or disseminated disease.
Candidosis	100 - 200 mg once daily	3 weeks - 7 months	Increase dose to 200 mg b.i.d. in case of invasive or disseminated disease.
Non-meningeal cryptococcosis	200 mg once daily	2 months - 1 year	
Cryptococcal meningitis	200 mg b.i.d.	2 months -1 year	Maintenance therapy: See Special Warnings and Special Precautions for Use.
Histoplasmosis	200 mg once daily - 200 mg b.i.d.	8 months	
Blastomycosis	100 mg once daily - 200 mg b.i.d.	6 months	
Lymphocutaneous and Cutaneous Sporotrichosis	100 mg once daily	3 months	
Paracoccidioidomycosis	100 mg once daily	6 months	Data on the efficacy of SPORANOX capsules at this dosage for treatment of paracoccidioidomycosis in patients with AIDS is not available.
Chromomycosis	100 – 200 mg once daily	6 months	
[1] The duration of treatment should be adjusted depending on the clinical response.			

Use in children

Clinical data on the use of SPORANOX capsules in pediatric patients are limited. SPORANOX capsules should not be used in children unless the potential benefit outweighs the potential risks. (“See Special Warnings and Special Precautions for Use.)”

Use in 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 Pharmacokinetic properties, Special populations, Hepatic

impairment)

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.

Contraindications

- SPORANOX capsules are contraindicated in patients with known hypersensitivity to itraconazole or to any of the excipients.
- Co-administration of the following drugs is contraindicated with SPORANOX capsules (See also Interaction with Other Medicinal Products and Other Forms of Interaction):
  - CYP3A4 metabolized substrates that can prolong the QT-interval e.g., astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with SPORANOX capsules. 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
- 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 Special warnings and special precautions for use.)
- SPORANOX capsules must not be used during pregnancy (except for life-threatening cases). See “Pregnancy and Lactation.”

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

Special Warnings and Special Precautions for Use

Cardiac effects

In a healthy volunteer study with SPORANOX IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. The clinical relevance of these findings to the oral formulations is unknown.

Itraconazole has been shown to have a negative inotropic effect and 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. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g., total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic

obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, SPORANOX should be discontinued.

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.

Interaction potential

SPORANOX has a potential for clinically important drug interactions. (See Interaction with other medicinal products and other forms of interaction).

Reduced gastric acidity

Absorption of itraconazole from SPORANOX capsules is impaired when gastric acidity is reduced. In patients also receiving acid neutralizing medicines (e.g. aluminium hydroxide) these should be administered at least 2 hours after the intake of SPORANOX capsules. 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.

Use in children

Clinical data on the use of SPORANOX capsules in pediatric patients is limited. SPORANOX capsules should not be used in pediatric patients unless the potential benefit outweighs the potential risks.

Hepatic effects

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 were 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.

Hepatic impairment

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. (See Pharmacokinetic properties, Special populations, Hepatic impairment)

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.

Cross-hypersensitivity

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.

Neuropathy

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

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 Interaction with other medicinal products and other forms of interaction, 3. Effect of itraconazole on the metabolism of other drugs). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Interactions with Other Medicinal Products and Other Forms of Interaction

1. Drugs affecting the absorption of itraconazole

Drugs that reduce the gastric acidity impair the absorption of itraconazole from SPORANOX capsules (see “Special Warnings and Special Precautions for Use”).

2. Drugs affecting the metabolism of itraconazole

Itraconazole is mainly metabolized through the cytochrome CYP3A4. Interaction studies have been performed with rifampicin, rifabutin and phenytoin, which are potent enzyme inducers of CYP3A4. Since the bioavailability of itraconazole and hydroxy-itraconazole was decreased in these studies to such an extent that efficacy may be largely reduced, the combination of itraconazole with these potent enzyme inducers is not recommended. No formal study data are available for other enzyme inducers, such as carbamazepine, phenobarbital and isoniazid, but similar effects should be anticipated.

Potent inhibitors of this enzyme such as ritonavir, indinavir, clarithromycin and erythromycin may increase the bioavailability of itraconazole.

3. Effect of itraconazole on the metabolism of other drugs

3.1 Itraconazole can inhibit the metabolism of drugs metabolized 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 concentrations decline gradually, depending on the dose and duration of treatment (see “Pharmacokinetic Properties”). This should be taken into account when the inhibitory effect of itraconazole on co-medicated drugs is considered.

Examples are:
The following drugs are contraindicated with itraconazole:

- Astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with SPORANOX 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

Caution should be exercised when co-administering itraconazole with calcium channel blockers due to an increased risk of CHF. In addition to possible pharmacokinetic interactions involving the drug metabolizing enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole.
The following drugs should be used with caution, and their plasma concentrations, effects or side effects should be monitored. Their dosage, if co-administered with itraconazole, should be reduced if necessary:

- Oral anticoagulants;
- HIV Protease Inhibitors such as indinavir, ritonavir and saquinavir;
- Certain antineoplastic agents such as busulphan, docetaxel, trimetrexate and vinca alkaloids;
- CYP3A4 metabolized calcium channel blockers such as dihydropyridines and verapamil;
- Certain immunosuppressive agents: cyclosporine, rapamycin (also known as sirolimus) and tacrolimus;
- Certain CYP3A4 metabolized HMG-CoA reductase inhibitors such as atorvastatin;
- Certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone;
- Digoxin (via inhibition of P-glycoprotein);
- Others: alfentanil, alprazolam, brotizolam, buspirone, carbamazepine, cilostazol, disopyramide, ebastine, eletriptan, fentanyl, halofantrine, midazolam IV, reboxetine, repaglinide, rifabutin.

3.2 No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed.
No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.
4. Effect on protein binding
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.
Pregnancy and Lactation
Use during Pregnancy
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 (see Contraindications).
In animal studies itraconazole has shown reproduction toxicity (see Preclinical Safety Data).
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 causal 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 candidosis – did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.
Women of childbearing potential
Women of childbearing potential taking SPORANOX capsules should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of SPORANOX therapy.
Lactation
A very small amount of itraconazole is excreted in human milk. 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.

Effects on Ability to Drive and Use Machines

No effects have been observed.

Undesirable Effects

Clinical trials
The table below shows the adverse events reported among patients in placebo-controlled trials (pooled data) of SPORANOX capsules, in the treatment of dermatomycosis and onychomycosis. It includes all adverse events (with an incidence of 1% or greater) reported among SPORANOX-treated patients. About 28% of patients treated with itraconazole and about 23% of patients treated with placebo experienced at least one adverse event. The adverse events reported are summarized irrespective of the causality assessment of the investigators.
The most frequently reported adverse events in clinical trials were of gastrointestinal origin.

Table 1: Adverse events reported among SPORANOX-treated patients with an incidence of ≥ 1%.

	SPORANOX N=929 %	PLACEBO N=661 %
Body as a Whole	**5.8**	**5.9**
Injury	2.9	3.0
Central and Peripheral Nervous System Disorders	**5.7**	**6.4**
Headache	4.0	5.0
Gastrointestinal disorders	**9.0**	**6.5**
Nausea	2.4	2.6
Diarrhea	2.3	2.0
Abdominal pain	1.8	1.4
Dyspepsia	1.7	0.9
Flatulence	1.3	0.5
Liver and biliary system disorders	**2.2**	**1.1**
Hepatic function abnormal	1.0	0.3
Respiratory System Disorders	**6.0**	**5.7**
Rhinitis	2.0	2.1
Upper respiratory tract infection	1.8	1.1
Sinusitis	1.7	1.2
Skin and Appendages Disorders	**5.1**	**2.1**
Rash	2.5	0.6

Post-marketing experience

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience with SPORANOX (all formulations) that meet threshold criteria are included in Table 2. The adverse drug reactions are ranked by frequency, using the following convention:

Very common ≥1/10

Common ≥1/100 and < 1/10

Uncommon ≥1/1000 and < 1/100

Rare ≥1/10000 and < 1/1000

Very rare < 1/10000, 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.

Table 2: Postmarketing Reports of Adverse Drug Reactions

Blood and lymphatic system disorders

Very rare: leukopenia, neutropenia, thrombocytopenia

Immune system disorders

Very rare: serum sickness; angioneurotic edema; anaphylactic, anaphylactoid and allergic reactions

Metabolism and nutrition disorders

Very rare: hypertriglyceridemia, hypokalemia

Nervous system disorders

Very rare: peripheral neuropathy, paraesthesia, hypoaesthesia, headache, dizziness

Table 2: Postmarketing Reports of Adverse Drug Reactions

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 edema, dyspnoea

Gastrointestinal disorders

Very rare: pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhea, 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, acute generalized exanthematous pustulosis, 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: edema, pyrexia

Overdose

No data are available.

In the event of an overdose, supportive measures should be employed. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate.

Itraconazole cannot be removed by hemodialysis.

No specific antidote is available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Itraconazole, a triazole derivative, has a broad spectrum of activity.

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

For itraconazole, breakpoints have only been established for *Candida* spp. from superficial mycotic infections (CLSI M27-A2, breakpoints have not been established for EUCAST methodology). The CLSI breakpoints are as follows: susceptible $\leq$0.125; susceptible, dose-dependent 0.25-0.5 and resistant $\geq$1 µg/mL. Interpretive breakpoints have not been established for the filamentous fungi.

In vitro studies demonstrate that itraconazole inhibits the growth of a broad range of

fungi pathogenic for humans at concentrations usually ranging from ≤ 0.025-0.8 µg/ml. These include:
dermatophytes (*Trichophyton spp., Microsporum spp., Epidermophyton floccosum*); yeasts (*Candida spp.*, including *C. albicans, Cryptococcus neoformans, Malassezia spp., Trichosporon spp., Geotrichum spp.); Aspergillus spp.; Histoplasma spp.; Paracoccidioides brasiliensis; Sporothrix schenckii; Fonsecaea spp.; Cladosporium spp.; Blastomyces dermatitidis; Coccidiodes immitis, Pseudallescheria boydii; Penicillium marneffei;* and various other yeasts and fungi.
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 resuling 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.

Pharmacokinetic Properties

General pharmacokinetic characteristics
The pharmacokinetics of itraconazole has been investigated in healthy subjects, special populations and patients after single and multiple dosing. In general, itraconazole is well absorbed. Peak plasma concentrations are reached within 2 to 5 hours following oral administration. Itraconazole undergoes extensive hepatic metabolism to give numerous metabolites. The main metabolite is hydroxyl-itraconazole, with plasma concentrations about twice those of the unchanged drug. The terminal half-life of itraconazole is about 17 hours after single dose and increases to 34 to 42 hours with repeated dosing. The pharmacokinetics of itraconazole is characterized by non-linearity and, consequently, shows accumulation in plasma after multiple dose administration. Steady-state concentrations are reached within 15 days, with C_{max} values of 0.5 µg/ml, 1.1 µg/ml and 2.0 µg/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 days. Itraconazole clearance decreases at higher doses due to a saturable mechanism of its hepatic metabolism. Itraconazole is excreted as inactive metabolites in urine (~35%) and in feces (~54%).
Absorption
Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.
Distribution
Most of the itraconazole in plasma is bound to protein (99.8%), with albumin being the main binding component (99.6% for the hydroxy-metabolite). It has also a marked

affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (> 700L), suggesting its extensive distribution into tissues: Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than the corresponding concentrations in plasma. Brain to plasma ratios were about 1.

The uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma.

Metabolism

Itraconazole is extensively metabolized by the liver into a large number of metabolites. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxyl-metabolite are about twice those of itraconazole.

As shown in *in vitro* studies, CYP3A4 is the major enzyme that is involved in the metabolism of itraconazole.

Excretion

Itraconazole is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with feces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas fecal excretion of unchanged drug varies between 3-18% of the dose.

As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeks after discontinuation of a 4-week treatment and in nail keratin – where itraconazole can be detected as early as 1 week after start of treatment – for at least six months after the end of a 3-month treatment period.

Special Populations

Hepatic impairment

Itraconazole is predominantly metabolized in the liver. A single oral dose (100 mg capsule) was administered to 12 patients with cirrhosis and six healthy control subjects; C_{max} AUC and terminal half-life of itraconazole were measured and compared between groups. Mean itraconazole C_{max} was reduced significantly (by 47%) in patients with cirrhosis. Mean elimination half-life was prolonged compared to that found in subjects without hepatic impairment (37 vs. 16 hours, respectively). Overall exposure to itraconazole, based on AUC was similar in cirrhotic patients and in healthy subjects. Data are not available in cirrhotic patients during long-term use of itraconazole. (See sections Posology and method of administration, and Special warnings and special precautions for use.)

Renal impairment

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

Preclinical Safety Data

Itraconazole has been tested in a standard battery of non-clinical safety studies.

Acute toxicity studies with itraconazole in mice, rats, guinea pigs and dogs indicate a wide safety margin. Sub (chronic) oral toxicity studies in rats and dogs revealed several target organs or tissues: adrenal cortex, liver and mononuclear phagocyte system as well as disorders of the lipid metabolism presenting as xanthoma cells in various organs.

At high doses, histological investigations of adrenal cortex showed a reversible swelling with cellular hypertrophy of the zona reticularis and fasciculata, which was sometimes associated with a thinning of the zona glomerulosa. Reversible hepatic changes were found at high doses. Slight changes were observed in the sinusoidal cells and vacuolation of the hepatocytes, the latter indicating cellular dysfunction, but without visible hepatitis or hepatocellular necrosis. Histological changes of the mononuclear phagosystem were mainly characterized by macrophages with increased proteinaceous material in various parenchymal tissues.
There are no indications of a mutagenic potential of itraconazole.
Itraconazole is not a primary carcinogen in rats or mice. In male rats, however, there was a higher incidence of soft-tissue sarcoma, which is attributed to the increase in non-neoplastic, chronic inflammatory reactions of the connective tissue as a consequence of raised cholesterol levels and cholesterosis in connective tissue.
There is no evidence of a primary influence on fertility under treatment with itraconazole. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats and mice at high doses. In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and macroglossia.
A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration.
In three toxicology studies using rats, itraconazole induced bone defects. The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility.

PHARMACEUTICAL PARTICULARS

List of Excipients

The inactive ingredients of the capsules are sugar spheres, hypromellose and macrogol (formulation F78).
The capsule itself contains titanium dioxide, indigotin disulphonate sodium, erythrosine sodium and gelatin.

Incompatibilities

None known

Shelf Life

Observe expiry date on the outer pack.

Special Precautions for Storage

Store between 15 and 30° C.
Keep out of reach of children.

Nature and Contents of Container

SPORANOX is available as pink and blue capsules, containing 100 mg of itraconazole in a pellet formulation, supplied in blister packs with 4, 6, 15 or 60 capsules.

Instructions for Use and Handling

Not applicable

DATE OF REVISION OF THE TEXT

September 2010