ITRANOX

Capsules

Composition

Each capsule contains :

Itraconazole	100 mg

Action

Itraconazole is a synthetic triazole derivative. When administered orally, it has shown fungistatic activity against superficial dermatophytes and *Candida* species including *C. albicans and C. glabrata.*

Itraconazole has shown antifungal activity against a variety of fungi and yeasts. This spectrum includes superficial dermatophytes (*Trichophyton* spp., *Microsporum*spp., *Epidermophyton floccosum*), yeasts (*Cryptococcus neoformans, Pityrosporum*spp., *Candida* spp. including *C. albicans*, *C. glabrata* and *C. krusei*), *Aspergillus* spp., *Histoplasma* spp., *Paracoccidioides brasiliensis, Sporothrix schenckii*, *Fonsecaea* spp., *Cladosporium* spp., *Blastomyces dermatitidis*.

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 itraconazole is maximal and appears to be more consistent when the capsules are taken immediately after a full 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 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. In contrast to the plasma levels, which become undetectable within 7 days of stopping therapy, therapeutic levels in the skin persist for 2 to 4 weeks after discontinuation of a 4-week treatment. Levels of itraconazole have been detected in the nail keratin as early as 1 week after start of treatment and persist for at least 6 months after the end of a 3-month course of therapy. Itraconazole is also present in sebum and to a lesser extent in sweat. 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.

Therapeutic levels in vaginal tissue are maintained for another 2 days after discontinuation of a 3-day course with 200 mg daily, and for another 3 days after discontinuation of a 1-day course with 200 mg b.i.d.

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 to itraconazole. Serum antifungal levels measured by bioassay were about 3 times those of itraconazole assayed by high performance liquid chromatography. Fecal excretion of the parent compound varies between 3-18% of the dose. Renal excretion of the parent compound is less than 0.03% of the dose. About 35% of a dose is excreted as metabolites in the urine within 1 week.

Indications

Itranox capsules are indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

- Blastomycosis, pulmonary and extrapulmonary;
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
- Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Itranox capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:

- Onychomycosis of the toenail with or without fingernail involvement due to dermatophytes (tinea unguium).
- Onychomycosis of the fingernail due to dermatophytes (tinea unguium)
- Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Contraindications

Itraconazole capsules are contra-indicated in pregnant women. Women of childbearing potential should take adequate contraceptive precautions during therapy and for one menstrual cycle after stopping therapy, as teratogenicity has been shown in laboratory animals.

Terfenadine, astemizole, mizolastine, cisapride, dofetilide, quinidine, pimozide, CYP3A4 metabolized HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam and triazolam should not be used during treatment with Itraconazole capsules.

Itraconazole capsules are also contra-indicated in patients with a known hypersensitivity to Itraconazole or its excipients, other azole antifungal agents or any of the excipients.

Itraconazole has been shown to have no benefit in the prophylaxis of Cryptococcal meningitis in HIV-infected patients.

Itraconazole should not be administered to treat onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF. Rare cases of CHF and pulmonary edema have been reported in the post-marketing period in patients treated with Itraconazole capsules. These patients were being treated for onychomycosis and/or systemic fungal infection. If signs or symptoms of CHF occur during administration of Itraconazole capsules, discontinue administration.

Warnings

Itraconazole is predominantly metabolized in the liver. The terminal half-life of Itraconazole in cirrhotic patients is somewhat prolonged. The oral bioavailability in cirrhotic patients is somewhat decreased. In such patients, as well as in other cases of hepatic impairment, it is advisable to monitor the Itraconazole plasma concentrations and to adapt the dose when necessary.

Cases of serious, usually reversible idiosyncratic hepatitis that may be fatal have been observed. Serious hepatotoxicity, including cases of fatal acute liver failure, has occurred with the use of Itraconazole. 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. These cases have been observed within the first week of treatment up to 1½ years after continuous use of Itraconazole. Liver function monitoring should be considered in patients receiving Itraconazole 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 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.

WARNING: Co-administration of terfenadine with Itraconazole is contra-indicated. Rare cases of 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 Sections.

Pharmacokinetic data indicate that another oral antifungal, Ketoconazole, inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole that may prolong QT intervals. *In vitro* data suggest 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.

Adverse Reactions

Approximately 9% of patients can be expected to experience adverse reactions while taking Itraconazole. In patients, receiving prolonged (approximately 1 month), continuous treatment especially, the incidence of adverse events was higher (about 15%). The most frequently reported adverse experiences were of gastrointestinal, hepatic, and dermatologic origin. Within each system organ class, the adverse reactions are ranked under headings of frequency using the following convention:

Very rare (<1/10,000)

The following adverse events have been reported:

• *Metabolism and Nutrition Disorders*
Very rare: hypokalemia.

• *Nervous System Disorders*
Very rare: peripheral neuropathy, headache, and dizziness.

• *Cardiac Disorders*
Very rare: congestive heart failure.

• *Respiratory, Thoracic and Mediastinal Disorders*
Very rare: pulmonary edema.

• *Gastrointestinal Disorders*
Very rare: abdominal pain, vomiting, dyspepsia, nausea, diarrhea and constipation

• *Hepato-Biliary Disorders*
Very rare: fatal acute liver failure, serious hepatotoxicity, hepatitis, and reversible increases in hepatic enzymes

• *Skin and Subcutaneous Tissue Disorders*
Very rare: Stevens-Johnson syndrome, angio-oedema, urticaria, alopecia, rash and pruritus.

• *Reproductive System and Breast Disorders*
Very rare: menstrual disorder.

• *General Disorders and Administrative Site Conditions*
Very rare: allergic reaction, and edema.

Less frequent cases of adrenal suppression have been reported, when high doses (600 mg/day) were given.

Precautions

General

Hepatic enzyme test values should be monitored in patients with preexisting hepatic function abnormalities. Hepatic enzyme test values should be monitored periodically in all patients receiving continuous treatment for more than one month or at any time; a patient develops signs or symptoms suggestive of liver dysfunction.

Itraconazole Capsules should be administered after a full meal under fasted conditions, Itraconazole absorption was decreased in the presence of decreased gastric acidity. The absorption of Itraconazole

may be decreased with the concomitant administration of antacids or gastric acid secretion suppressors. Studies conducted under fasted conditions demonstrated that administration with 8 ounces of a cola beverage resulted in increased absorption of Itraconazole in AIDS patients with relative or absolute achlorhydria. This increase relative to the effects of a full meal is unknown.

Paediatric Use
The efficacy and safety of Itraconazole have not been established in pediatric patients. No pharmacoki*netic* data on capsules are available in children. A small number of patients age 3 to 16 years have been treated with 100 mg/day of Itraconazole capsules for systemic fungal infection and no serious unexpected adverse effects have been reported.

While no such bone toxicity has been reported in adult patients, the long-term effect of Itraconazole in paediatric patients is unknown.

HIV-infected Patients
Because hypochlorhydria has been reported in HIV-infected individuals, the absorption of Itraconazole in these patients may be decreased.

Drug Interactions

Both Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of the cytochrome P450 3A enzyme system. Co administration of Itraconazole and drugs primarily metabolized by the cytochrome P450 3A enzyme system may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects.
Therefore unless otherwise specified, concomitant medications metabolized by the P450 3A enzyme system should be discontinued as medically indicated.

Selected drugs that are predicted to have plasma concentrations increased by Itraconazole +

- Anticoagulants: warfarin
- Antihistamines: terfenadine*, astemizole*
- Anti-HIV protease inhibitors: ritonavir, indinavir
- Antineoplastic agents: vinca alkaloids
- Benzodiazepines: midazolam*, triazolam*, diazepam
- Calcium channel blockers: dihydropyridines
- Cholesterol-lowering agents: lovastatin*, simvastatin*
- GI motility agents: cisapride*
- Immunosuppressive agents: cyclosporine, tacrolimus
- Steroids: methylprednisolone
- Other: digoxin, quinidine

+ This table is not all-inclusive.
* Specifically contraindicated with Itraconazole based on clinical and/or pharmacokinetics studies

Selected Drugs that are predicted to Decrease Itraconazole Plasma Concentrations:

Anticonvulsants
Phenytoin, phenobarbital, carbamazepine. Reduced plasma concentrations of Itraconazole were reported when Itraconazole was co administered with phenytoin. The physician is advised to monitor the plasma concentrations of Itraconazole when phenytoin is taken concurrently, and to increase the dose of Itraconazole if necessary.

Antimycobacterial agents
Isoniazid, rifampin, rifabutin

Anticoagulants

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.

Antihistamines
Co administration of terfenadine with Itraconazole has led to elevated plasma concentrations of terfenadine, resulting in rare instances of life-threatening cardiac dysrhythmia and death. Co administration of astemizole with Itraconazole has led to elevated plasma concentrations of astemizole and desmethylastemizole that may prolong the QT intervals. Therefore, concomitant administration of Itraconazole with astemizole is contraindicated.

Anti-HIV protease inhibitors
Co administration of Itraconazole with protease inhibitors primarily metabolized by the cytochrome P450 3A enzyme system. Such as ritonavir or indinavir, may result in changes in plasma concentrations of both drugs. Caution is advised when these drugs are used concomitantly.

Anti-HIV reverse transcriptase inhibitors
The results from a study in which eight HIV-infected individuals were treated with zidovudine, 8 ± 0.4 mg/kg/day, showed that the Pharmacokinetics of zidovudine were not affected during concomitant administration of Itraconazole Capsules, 100 mg b.i.d. Other agents have not been studied.

Antimycobacterial agents
Plasma concentrations of azole antifungal agents are reduced when given concurrently with isoniazid or rifampin. Alternative antifungal therapy should be considered if isoniazid or rifampin therapy is necessary. A similar effect may be expected with rifabutin.

Antineoplastic agents
Itraconazole may inhibit the metabolism of vinca alkaloids therefore, patients receiving Itraconazole concomitantly with vinca alkaloids should be monitored for an increase and/or prolongation of the effects of the latter drug product including adverse effects such as peripheral neuropathy and ileus, and the dose of the vinca alkaloid should be adjusted appropriately.

Benzodiazepines
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 and patient monitoring is required since the sedative effect may be prolonged.

Calcium channel blockers
Edema has been reported in patients concomitantly receiving Itraconazole and dihydropyridine calcium channel blockers. Appropriate dosage adjustments may be necessary.

Cholesterol lowering agents
Human pharmacokinetic data indicate that Itraconazole inhibits the metabolism of lovastatin resulting in significantly elevated plasma concentrations of lovastatin or lovastatin acid that have been associated with rhabdomyolysis. Use of HMG-CoA reductase inhibitors metabolized by the P450 3A enzyme system, such as lovastatin or simvastatin should be temporarily discontinued during Itraconazole therapy.

Digoxin
Co administration of Itraconazole and digoxin has led to increased plasma concentrations of digoxin. Digoxin concentrations should be monitored at the initiation: of Itraconazole therapy and frequently thereafter, and the dose of digoxin should be adjusted appropriately.

GI motility agents

Human pharmacokinetic data indicate that oral ketoconazole potently inhibits the metabolism of cisapride resulting in significantly elevated plasma concentrations 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.

H2 antagonists
Reduced plasma concentrations of Itraconazole were reported when Itraconazole capsules were co administered with H2 antagonists.

Immunosuppressive agents
Co administration of Itraconazole and cyclosporine or tacrolimus has led to increased plasma concentrations of the latter two agents. Cyclosporine and tacrolimus concentrations should be monitored at the initiation of Itraconazole therapy and frequently thereafter, and the dose of cyclosporine or tacrolimus should be adjusted appropriately.

Oral hypoglycemic agents
Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when Itraconazole and oral hypoglycemic agents are co-administered.

Quinidine
Tinnitus and decreased hearing have been reported in patients concomitantly receiving Itraconazole and quinidine.

Steroids
Itraconazole may inhibit the metabolism of methylprednisolone, therefore, patients receiving Itraconazole concomitantly with methylprednisolone should be monitored for an increase and/or prolongation of the effects of the latter drug product, including adverse effects, and the dose of methylprednisolone should be adjusted appropriately.

Dosage and Administration

Itranox capsules should be taken immediately after a meal for optimal absorption.

Dosage recommendations vary according to the infection treated:

<table>
<tr><th>Indication</th><th colspan="2">Dose</th><th>Median duration</th></tr>
<tr><td>Vulvovaginal candidosis</td><td colspan="2">200 mg twice daily</td><td>1 day</td></tr>
<tr><td>Dermatomycosis</td><td colspan="2">200 mg daily
or 100 mg daily</td><td>7 days
or 15 days</td></tr>
<tr><td colspan="4">Highly keratinized regions as in plantar tinea pedis and palmar tinea manus require 100 mg daily for 30 days, or 200 mg twice daily for 7 days</td></tr>
<tr><td>Fungal keratitis</td><td colspan="2">200 mg daily</td><td>21 days</td></tr>
<tr><td colspan="4">Onychomycosis
Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.</td></tr>
<tr><td>(continuous treatment)</td><td>200 mg daily</td><td colspan="2">3 months</td></tr>
<tr><td>(pulse treatment)</td><td>200 mg twice daily</td><td colspan="2">1-week
Fingernail infections: 2 pulse treatments.
Toenail infections: 3 pulse treatments.
Pulse treatments are always separated by a 3 week drug-free interval.
See table below.</td></tr>
</table>

Site of onychomycosis	Week 1	Weeks 2, 3 and 4	Week 5	Weeks 6, 7 and 8	Week 9
Toenails with or without fingernail involvement	**Pulse 1** 200 mg twice daily	Itraconazole free week	**Pulse 2** 200 mg twice daily	Itraconazole free week	**Pulse 3** 200 mg twice daily
Fingernails only	**Pulse 1** 200 mg twice daily	Itraconazole free week	**Pulse 2** 200 mg twice daily		

Elimination of Itraconazole from skin and nail is slower than from plasma. Optimal clinical mycological effects are thus reached 1 to 4 weeks after the cessation of treatment for skin infections and 6 to 9 months after cessation of treatment for nail infections.

Dosages that have been used in systemic mycoses:

Indication	Dose	Median duration	Remarks
Aspergillosis	200 mg daily	2 - 5 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease.
Candidiasis (excluding vulvovaginal)	100-200 mg daily	3 weeks - 7 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease.
Histoplasmosis (excluding meningeal histoplasmosis)	200 mg daily - 200 mg twice daily (or 400 mg once daily)	8 months	
Sporotrichosis	100 mg daily	3 months	
Paracoccidio- idomycosis	100 mg daily	6 months	
Chromomycosis	100 - 200 mg daily	6 months	
Blastomycosis	100 mg daily - 200 mg twice daily (or 400 mg once daily)	6 months	

In children (below 12 years): Itranox capsules have not been systematically studied in children.
In elderly: As for use in children.

Data from a small number of HIV-infected patients suggested that the response rate of histoplasmosis in HIV-infected patients is similar to non-HIV-infected patients. The clinical course of histoplasmosis in HIV-infected patients is more severe and usually requires maintenance therapy to prevent relapse. The optimal dosage regimen for treatment and maintenance therapy are unknown. Studies to investigate the efficacy and safety of Itranox , including optimal dosage and duration in HIV-infected patients are ongoing.

Over Dosage

Itraconazole is not removed by dialysis. In the event of accidental over dosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

There are limited data on the outcomes of patients ingesting high doses of Itraconazole. In patients taking up to 3000 mg of Itraconazole Capsules, the adverse event profile was similar to that observed at recommended doses.

Presentation
Box of 4 or 14 capsules