

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

General pharmacokinetic characteristics

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 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. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

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 capsule dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H₂-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases. Absorption of itraconazole under fasted conditions in these subjects is increased when Itraconazole Capsules are administered with an acidic beverage (such as a non-diet cola). When Itraconazole Capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H₂-receptor antagonist, itraconazole absorption was comparable to that observed when Itraconazole Capsules were administered alone.

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given.

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 (> 700 L), 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 corresponding concentrations in plasma, and the uptake into keratinous tissues, skin in particular, is

up to four times higher than in plasma. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

Metabolism

Itraconazole is extensively metabolised by the liver into a large number of metabolites. *In vitro* studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to Itraconazole; trough plasma concentrations of the hydroxy-itraconazole are about twice those of itraconazole.

Excretion

Itraconazole is excreted mainly as inactive metabolites in urine (35%) and faeces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, faecal excretion of unchanged drug varies between 3 – 18% of the dose.

Special Populations

Hepatic Impairment:

Itraconazole is predominantly metabolised in the liver. A pharmacokinetic study using a single 100 mg dose of itraconazole (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. A statistically significant reduction in average C_{max} (47%) and a two fold increase in the elimination half-life (37 ± 17 versus 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC, was similar in cirrhotic patients and in healthy subjects.

Data are not available in cirrhotic patients during long-term use of itraconazole.

Renal Impairment:

Limited data are available on the use of oral itraconazole in patients with renal impairment. A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of $13 \text{ ml/min} \times 1.73 \text{ m}^2$, the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max} , C_{max} , and AUC_{0-8h}). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50-79 ml/min), moderate (defined in this study as CrCl 20-49 ml/min), and severe renal impairment (defined in this study as CrCl <20 ml/min) were similar to that in healthy subjects, (range of means 42-49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively.) Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole.

Paediatrics

Limited pharmacokinetic data are available on the use of itraconazole in the paediatric population. Clinical pharmacokinetic studies in children and adolescents aged between 5 months and 17 years were performed with itraconazole capsules, oral solution or intravenous formulation. Individual doses with the capsule and oral solution formulation ranged from 1.5 to 12.5 mg/kg/day, given as once-daily or twice-daily administration. The intravenous formulation was given either as a 2.5 mg/kg single infusion, or a 2.5 mg/kg infusion given once daily or twice daily. For the same daily dose, twice daily dosing compared to single daily dosing yielded peak and trough concentrations comparable to adult single daily dosing. No significant age dependence was observed for itraconazole AUC and total body clearance, while weak associations between age and itraconazole distribution volume, C_{max} and

terminal elimination rate were noted. Itraconazole apparent clearance and distribution volume seemed to be related to weight.

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 cavitory 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 pharmacokinetic 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:

Indication	Dose	Median duration
Vulvovaginal candidosis	200 mg twice daily	1 day
Dermatomycosis	200 mg daily or 100 mg daily	7 days or 15 days
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		
Fungal keratitis	200 mg daily	21 days
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.		
(continuous treatment)	200 mg daily	3 months
(pulse treatment)	200 mg twice daily	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.
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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