

Data Sheet

Itcozol™

itraconazole 100 mg capsule

Presentation

Size 0 capsule with a green opaque cap and body containing beads.

Uses

Actions

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 in vitro 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 *in vitro* to itraconazole. Serum antifungal levels measured by bioassay were about 3 times those of itraconazole assayed by high performance liquid chromatograph. Faecal 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

ITCOZOL capsules are indicated for the treatment of:

- vulvovaginal candidiasis.
- pityriasis versicolor, dermatomycosis, fungal keratitis, oral candidiasis.
- onychomycosis caused by dermatophytes and/or yeasts.
- systemic mycoses, including aspergillosis and non-invasive systemic candidiasis (without underlying immunosuppression), histoplasmosis, sporotrichosis, paracoccidioidomycosis, blastomycosis, and other rarely occurring systemic or tropical mycoses.

Dosage and Administration

For optimal absorption, it is essential to administer ITCOZOL capsules immediately after a full meal. The capsules must be swallowed whole. Treatment schedules are as follows:

Indication	Dose	Duration
Vulvovaginal candidiasis	200 mg twice daily	1 day
	or 200 mg once daily	3 days
Pityriasis versicolor	200 mg once daily	7 days
Dermatomycosis	100 mg once daily	15 days
	or 200 mg once daily	or 7 days
Highly keratinised regions as in plantar tinea pedis and palmar tinea manus require an additional treatment of 15 days at 100 mg daily.		
Oral candidiasis	100 mg once daily	15 days
In some immunocompromised patients, e.g. neutropenic, AIDS or organ transplant patients, the oral bioavailability of itraconazole may be decreased. Therefore, the doses may need to be doubled.		
Fungal keratitis	200 mg once daily	21 days

Onychomycosis

- Pulse treatment (see table below):

A pulse treatment consists of two capsules twice daily (200 mg bid) 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 treatment-free interval. Clinical response will become evident as the nail regrows, following discontinuation of the treatment.

Site of onychomycosis	Week 1	Weeks 2, 3, 4	Week 5	Weeks 6, 7, 8	Week 9
Toenails with or without fingernail involvement	Pulse 1	ITCOZOL-free	Pulse 2	ITCOZOL-free	Pulse 3
Fingernails only	Pulse 1	ITCOZOL-free	Pulse 2	ITCOZOL-free	-

- Continuous Treatment: 200 mg once daily for 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

Dosage recommendations for systemic mycoses vary according to the infection treated and are as follows:

Indication	Dose	Median duration	Remarks
Aspergillosis	200 mg once daily	2-5 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease
Non-invasive systemic candidiasis	100-200 mg once daily	3 weeks-7 months	
Histoplasmosis	200 mg once daily to 200 mg twice daily	8 months	
Sporotrichosis	100 mg once daily	3 months	
Paracoccidioidomycosis	100 mg once daily	6 months	
Chromomycosis	100-200 mg once daily	6 months	
Blastomycosis	100mg once daily - 200mg twice daily	6 months	

Contraindications

ITCOZOL capsules are contraindicated in patients who have shown hypersensitivity to itraconazole or the excipients.

ITCOZOL capsules are contraindicated in pregnant women except for the treatment of systemic mycoses, where the potential advantages must be weighed against the potential harm to the foetus. Adequate contraceptive precautions should be used by women of childbearing potential throughout ITCOZOL therapy, and continued until the next menstrual period following the end of ITCOZOL therapy.

Coadministration of 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) with ITCOZOL is contraindicated.

ITCOZOL 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 **WARNING AND PRECAUTIONS**).

Warnings and Precautions

ITCOZOL has a potential for clinically important interactions with other medicines (see **INTERACTIONS**).

Congestive heart failure

In a study with itraconazole 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. Itraconazole 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.

ITCOZOL 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 ITCOZOL, 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. ITCOZOL 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 ITCOZOL and calcium channel blockers due to an increased risk of CHF.

Decreased gastric acidity

Absorption of itraconazole from ITCOZOL 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 ITCOZOL 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 ITCOZOL capsules with a cola beverage.

Hepatic impairment

Itraconazole is predominantly metabolised 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. Dose adjustments may be considered in these patients.

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have 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. 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 ITCOZOL 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 an 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.

Renal impairment

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

Peripheral neuropathy

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

Other azole antifungal agents

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

Immunocompromised patients

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

Patients with immediately life-threatening systemic fungal infections

Due to the pharmacokinetic properties ITCOZOL 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 therapy.

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). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Use in children

The efficacy and safety of ITCOZOL capsules have not been established in children. Since clinical data for the use of itraconazole in children is limited, ITCOZOL 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 **FURTHER INFORMATION - Toxicology**).

Pregnancy and lactation

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.

ITCOZOL capsules should not be used during 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 ITCOZOL 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 itraconazole has not been established.

Epidemiological data on exposure to itraconazole 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 itraconazole should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of itraconazole 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 ITCOZOL 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 on ability to drive or to use machinery have been observed.

Adverse Effects

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.
Endocrine	menstrual disorder

Very rare (<0.01%)

Liver	hepatitis (especially during prolonged treatment)
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Postmarketing experience

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

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

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

Interactions

1. Drugs affecting the absorption of itraconazole

Drugs that reduce the gastric acidity impair the absorption of itraconazole from ITCOZOL capsules (see **WARNINGS and PRECAUTIONS**).

2. Medicines affecting the metabolism of itraconazole

Itraconazole is mainly metabolised 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. Effects of itraconazole on the metabolism of other medicines

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

Examples are:

The following drugs are contraindicated with itraconazole:

- Terfenadine, astemizole, bepridil, cisapride, levacetylmethadol (levomethadyl), mizolastine, dofetilide, quinidine, pimozide and sertindole are contraindicated with ITCOZOL 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 metabolised HMG-CoA reductase inhibitors, such as simvastatin and lovastatin.
- Triazolam and oral midazolam.

- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).
- Nisoldipine.

Caution should be exercised when co-administering ITCOZOL with calcium channel blockers. 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 ITCOZOL.

The following drugs should be used with caution, and their plasma concentrations, effects or side effects should be monitored. Their dosage, if coadministered with ITCOZOL, should be reduced if necessary:

- Oral anticoagulants
- HIV protease inhibitors, such as ritonavir, indinavir, saquinavir
- Certain antineoplastic agents, such as vinca alkaloids, busulphan, docetaxel and trimetrexate
- CYP3A4 metabolised calcium channel blockers, such as dihydropyridines and verapamil
- Certain immunosuppressive agents, such as cyclosporin, tacrolimus, sirolimus
- Certain CYP3A4 metabolised HMG-CoA reductase inhibitors such as atorvastatin.
- Certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone.
- Others: digoxin, carbamazepine, buspirone, alfentanil, alprazolam, brotizolam, cilostazol, disopyramide, midazolam IV, rifabutin, ebastine, eletriptan, fentanyl, halofantrine, reboxetine and repaglinide.

No interaction of itraconazole with zidovudine (AZT) and fluvastatin have been observed. No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

4. Effects 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.

Overdosage

Treatment

No data are available. In the event of accidental overdosage, 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 haemodialysis. No specific antidote is available.

Pharmaceutical Precautions

Shelf Life

2 years when stored below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

Blisters in a carton of 15 capsules.

Further Information

ITCOZOL capsules contain sucrose, starch, hypromellose and poloxamer. The capsule is made of gelatin and also contains titanium dioxide, indigo carmine and quinoline yellow.

Carcinogenesis, mutagenicity, impairment of fertility

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

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

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

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.

Microbiology

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 <0.125; susceptible, dose-dependent 0.25-0.5 and resistant >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 ≤ 1 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*; *Coccidioides immitis*; *Pseudallescheria boydii*; *Penicillium marneffeii*; 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 14 α -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.

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