ITRAZOL®

Description
ITRAZOL® is asynthetic broad-spectrum antifungal agent available in pink and blue capsules, each containing 100 mg itraconazole in a pellet formulation supplied in blister packs with either 4, 15 capsules. The inactive ingredients of the capsules are hydroxypropyl-methylcellulose 2930, poloxamer (Lutrol), saccharose, corn starch, methylene chloride and ethyl alcohol.

Properties
Pharmacodynamics: Itraconazole, triazole derivative, is active against infections with 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., Blatomyces dermatitidis, and various other yeasts and fungi.
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 tis systhesis ultimately results in an antifungal effect.
Pharmacokinetics: The oral bioavailability of itraconazole is maximal when the capsules are taken immediately after a full meal. Peak plasma levels are reached 3 to 4 hours following an oral dose. Elimination from plasma is biphasic with a terminal half-life of 1 to 1.5 days. During chronic administration, steady-state is reached after 1-2 weeks. Steady-state plasma concentrations of itraconazole 3-4 hours after drug intake are 0.4 µg/ml (100 mg o.d.), 1.1 µg/ml (200 mg o.d.) and 2.0 µg/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. Uptake in keratinous tissues, especially the skin, is up to 4 times higher than in plasma, and elimination of itraconazole is related to epidermal regeneration. In contrast to the plasma levels which become undetectable within 7 days of stopping therpy, 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 also extensively distributed into tissues that are prone to fungal invasion. 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 metabolized 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. Antifungal drug levels measured by bio-assay were about 3 times those of itraconazole assayed by high-performacne liquid chromatography. Faecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 35% of a dose is excreted as metabolites in the urine within 1 week.

Indications
ITRAZOL® capsules is indicated for the treatment of the following conditions:
– Gynaecological indications: Vulvovaginal candidosis.
– Dermatological/ophthalmological indications:
  - Pityriasis versicolor, dermatomycosis, fungal keratitis and oral candidosis.
  - Onychomycosis, caused by dermatophytes and/or yeast.
– Systemic mycoses: Systemic aspergillosis and candidosis, cryptococcosis (including cryptococcal meningitis), histoplasmosis, sporotrichosis, paracoccidioidomycosis, blastomycosis, and other rarely occurring systemic or tropical mycoses.

Contraindications
– ITRAZOL® capsules is contraindicated in patients with a known hypersensitivity to the drug or its excipients.
  ITRAZOL® capsules should only be given to pregnant women in lifethreatening cases and when in these cases the potential benefit outweighs the potential harm to the foetus. Adequate contraceptive precautions should be taken by women of child-bearing potential using ITRAZOL® capsules until the next menstrual period following the end of ITRAZOL® therapy.
– Terfenadine, astemizole, mizolastine, cisapride, dofetilide, quinidine, pimozide, CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin triazolam and oral midazolam are contra-indicated with ITRAZOL® capsules.

Warnings and precautions:
– In a healthy volunteer study with Itraconazole 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 Itraconazole has been associated with reports of congestive heart failure. ITRAZOL® 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, 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, ITRAZOL® should be discontinued.
– Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers.
– ITRAZOL® has a potential for clinically important drug interaction. (see interaction with other medicaments and other forms of interaction).
– Decreased gastric acidity: Absorption of itraconazole from ITRAZOL® 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 ITRAZOL® capsules. In patients with achlorhydira such as certain AIDS patients and patients on acid secretion suppressors (e.g. H_2-antagonists, protonpump inhibitors) it is advisable to administer ITRAZOL® capsules with a cola beverage.
– Paediatric use: Since clinical data of the use of Itrazol capsules in paediatric patients is limited, ITRAZOL® capsules should not be used in these patients unless the potential benefit outweighs the potential risks.
– Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Itraconazol. 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 ITRAZOL® 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: 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. A dose adjustment may be considered.
– Renal impairment: The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. A dose adjustment may be considered.
– If neuropathy occurs that may be attributed to ITRAZOL® capsules, the treatment should be discontinued.
– There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be taken in prescribing ITRAZOL® capsules to patients with hypersensitivity to other azoles.

Interactions
– Drugs affecting the metabolism of itraconazole:
Interaction studies have been performed with rifampicin, rifabutin and phenytoin. Since the bioavailability of itraconazole and hydroxyitraconazole 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 isoniasid, but similar effects should be anticipated.
As itraconazole is mainly metabolised through CYP3A4, potent inhibitors of this enzyme may increase the bioavailability of itraconazole. Examples are: ritonavir, indinavir, clarithromycin and erythromycin.

– Effect of itraconazole on the metabolism of other drugs:
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. After stopping treatment, itraconazole plasma level decline gradually, depending on the dose and duration of treatment (see pharmacokinetic properties). This should be taken into consideration when the inhibitory effect of itraconazole on comedicated drugs is considered.
Examples are:
Drugs which should not be used during treatment with itraconazole:
Terfenadine, astemizole, mizolastine, cisapride, triazolam, oral midazolam, dofetilide, quinidine, pimozide, CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin. Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be taken when co-administering itraconazole and calcium channel blockers.
Drugs whose plasma levels, 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 ritonavir, indinavir, saquinavir;
– Certain Antineoplastic Agents such as vica alkaloids, busulphan, docetaxel and trimetrexate.
– CYP3A4 metabolised Calcium Channel Blockers such as dihydrophyridines and verapamil.
– Certain Immunusuppressive Agents: cyclosporine, tacrolimus, rapamycin (also known as sirolimus).
– Others; digoxin, carbamazepine, buspirone, alfentanil, alprazolam, brotizolam, midazolam IV, rifabutin, methylprednisolone ebastine, reboxetine.
– No interaction of itraconazole with AZT (zidovudine) and fluvastatine has been observed.
– No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

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.
Pregnancy and lactation
– When administered at high doses to pregnant rats (40 mg/kg/day or higher) and mice (80 mg/kg/day or higher), itraconazole was shown to increase the incidence of fetal abnormalities and did produce adverse effects on the embryo, studies on the use of itraconazole in pregnant women are not available. Therefore, ITRAZOL® capsules should only be given in life-threatening cases of systemic mycosis and when in these cases the potential benefit outweighs the potential harm to the foetus.
– A very small amount of itraconazole is excreted in human milk.The expected benefits of ITRAZOL® capsules therapy should therefore be weighed against the potential risk of breastfeeding. In case of doubt the patient should not breast-feed.

Effects on driving ability and use of machinery
No effects have been observed.

Dosage and administration
For optimal absorption, it is essential to administer ITRAZOL® capsules immediately after a full meal.
The capsules must be swallowed whole.

Indication	Dose	Duration
Gynaecological indications • Vulvovaginal candidosis	200 mg b.i.d. or 200 mg o.d.	1 day 3 days
Dermatological / ophthalmological indications • Pityriasis versicolor	 200 mg o.d.	 7 days
• Dermatomycosis	200 mg o.d. or 100 mg o.d.	7 days or 15 days
Highly keratinized regions as in plantar tinea pedis and palmar tinea manus require 200 mg twice daily for 7 days, or 100 mg daily for 30 days		
• Oral candidosis	100 mg o.d.	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 doubling.		
• Fungal keratitis	200 mg o.d.	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 drug-free interval. Clinical response will become evident as the nail regrows, following discontinuation of the treatment.

Site of onychomycosis	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Toenails with or without fingernail involvement	Pulse 1	itraconazole free weeks			Pulse 2	itraconazole free weeks			Pulse 3
Fingernails only	Pulse 1	itraconazole free weeks			Pulse 2				

OR
- continuous treatment:
Two capsules daily (200 mg o.d.) 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.

Indication	Dose	Median duration	Remarks
Aspergillosis Candidosis	200 mg o.d. 100-200 mg o.d.	2-5 months 3 weeks-7 months	increase dose to 200 mg b.i.d. in case of invasive or disseminated disease
Non-meningeal cryptococcosis Cryptococcal meningitis	 200 mg o.d. 200 mg b.i.d.	 2 months-1 year	 Maintenance therapy: (meningeal cases) 200 mg o.d.
Histoplasmosis Sporotrichosis Paracoccidioidomycosis Chromomycosis Blastomycosis	200 mg o.d.-200 mg b.i.d. 100 mg o.d. 100 mg o.d. 100-200 mg o.d. 100 mg o.d.-200 mg b.i.d.	8 months 3 months 6 months 6 months 6 months	

Adverse reactions
The most frequently reported adverse experiences in association with the use of Itraconazole were of gastro-intestinal origin, such as dyspepsia, nausea, vomiting, diarrhoea, abdominal pain and constipation. Other reported adverse experiences include headache, reversible increases in hepatic enzymes, hepatitis, menstrual disorder, dizziness and allergic reactions (such as pruritus, rash, urticaria and angio-oedema), peripheral neuropathy, Stevens-Johnson syndrome, alopecia, hypokalaemia, oedema, congestive heart failure and pulmonary oedema. Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Itraconazole.

Overdosage
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.

How supplied
ITRAZOL® is available as capsules, containing 100 mg of itraconazole in a pellet formulation, supplied in blister packs with either 4 or 15 capsules.

Storage conditions
ITRAZOL® capsules must be stored below 30°C.

Manufactured by:
SAJA Pharmaceutical Co., Ltd.
Saudi Arabian Japanese Pharmaceutical Company

THIS IS A MEDICAMENT
- A drug is a product which acts on your health and its consumption could be dangerous when you do not follow the instructions.
- Follow strictly the doctor's prescriptions, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist know the medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep out of the reach of children.

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