Tracon® Capsules

Itraconazole

QUALITATIVE AND QUANTITATIVE COMPOSITION:

Tracon is a synthetic broad-spectrum antifungal agent available in capsules form, each containing 100 mg itraconazole.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamics

Itraconazole, a 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., Blastomyces 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 its synthesis 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 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 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. 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.

CLINICAL PARTICULARS:

Therapeutic Indications:

Tracon 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 yeasts.

• Systemic mycoses :

Systemic aspergillosis and candidosis, cryptococcosis (including cryptococcal meningitis), histoplasmosis, sporotrichosis, paracoccidioidomycosis, blastomycosis, and other rarely occurring systemic or tropical mycoses.

CONTRAINDICATIONS :

• **Tracon** capsules is contra-indicated in patients with a known hypersensitivity to the drug or its excipients.

• **Tracon** capsules should only be given to pregnant women in life-threatening 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 **Tracon** capsules until the next menstrual period following the end of **Tracon** therapy.

• Cisapride, terfenadine, mizolastine, dofetilide, quinidine, pimozide, levacetylmethadol, CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin, triazolam and oral midazolam are contra-indicated with **Tracon** capsules.

SPECIAL WARNING & SPECIAL PRECAUTION FOR USE:

• Itraconazole has been shown to have a negative inotropic effect and Itraconazole has been associated with reports of congestive heart failure, **Tracon** should not be used in the treatment of onychomycosis 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, **Tracon** 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.

• **Tracon** 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 **Tracon** 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 **Tracon** capsules. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (e.g. H2-antagonists, protonpump inhibitors) it is advisable to administer **Tracon** capsules with a cola beverage.

• **Paediatric use :** Since clinical data of the use of Itraconazole capsules in paediatric patients is limited, **Tracon** 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 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.

• 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 attributable to **Tracon** capsules, the treatment should be discontinued.

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

INTERACTION WITH OTHER MEDICAL PRODUCTS AND OTHER FORMS OF INTERACTION:

• 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 isoniazid, 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 account when the inhibitory effect of itraconazole on comedicated drugs is considered.

Example are :

Drugs which should not be used during treatment with itraconazole:

Terfenadine, mizolastine, 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 used 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 dihydropyridines and verapamil.

• Certain Immunosuppressive 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.

PREGNANCY AND LACTATION :

• Studies on the use of itraconazole in pregnant women are not available. Therefore, **Tracon** 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 **Tracon** 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.

POSOLOGY AND METHOD OF ADMINISTRATION:

For optimal absorption, it is essential to administer **Tracon** 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 b.i.d.) for one week. Two pulse treatments are recommended for fingernail infections, and three pulse treatments for toenail infections. Pulse treatments are always separated by a 3-week drug-free interval. Clinical response will become evident as the nail 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 (see table below) :

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

UNDESIRABLE EFFECTS:

The most frequently reported adverse experiences in association with the use of **Tracon** 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.

OVERDOSAGE :

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 PARTICULARS:

List of excipients: Hydroxypropyl methylcellulose, sugar spheres, methylene chloride, isopropyl alcohol and gelatin capsule.

STORAGE :

Tracon capsules must be stored below 30˚C.

AVAILABILITY:

Tracon is available as capsules, containing 100 mg of itraconazole.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacists who sold the medicament.
- The doctor and the pharmacists are experts in 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 medicaments out of the reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Manufactured by **SPIMACO**
Al-Qassim Pharmaceutical Plant
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