1.6 Product Information

1.6.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

(SPC, CONTAINER LABELING & PATIENT INFORMATION LEAFLET, MOCK-UPS AND SPECIMENS)

SPC – Summary of the Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

INTRAZ (Itraconazole Capsules 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Itraconazole Capsules 100 mg.

3. PHARMACEUTICAL FORM

Dosage form: Capsule.
Description: A Scarlet/ Scarlet coloured hard gelatin capsule size '0' unprinted containing off white spherical pellets.

4.1 Therapeutic indications

- Vulvovaginal candidiasis,
- Oral candidiasis
- Dermatophytoses caused by organisms susceptible to Itraconazole (Trichophyton spp., Microsporum spp., Epidermophyton floccosum) e.g. tinea pedis, tinea cruris, tinea corporis, tinea manuum,
- Pityriasis versicolor,
- Onychomycoses caused by dermatophytes and/or yeasts,
- Systemic candidiasis,
- Cryptococcal infections (including cryptococcal meningitis). In immunosuppressed patients suffering from cryptococcosis and in patients with cryptococcosis of the CNS ITRACONAZOLE is indicated only if the usually recommended initial therapy seems to be inappropriate or ineffective
- Histoplasmosis.
- Aspergillosis. ITRACONAZOLE can be used to treat patients suffering from invasive aspergillosis who were found to be refractory or intolerant to Amphotericin B
- Maintenance therapy in AIDS patients to prevent relapse of underlying fungal infection who were found to be refractory or intolerant to first-line systemic anti-fungal therapy is inappropriate or has proved ineffective.

Due to PK properties, orally administered ITRACONAZOLE (capsules) should not be used as the initial treatment in patients with severe life-threatening forms of systemic mycoses. Oral forms should be used as a continuation therapy, after initial treatment with i.v. ITRACONAZOLE.

Consideration should be given to official guidance regarding the appropriate use of antifungal agents.

4.2 Posology and method of administration

Paediatric population

ITRACONAZOLE should not be administered to children as there is limited clinical data describing the pediatric use of this drug.

Elderly patients

Not recommended

Patients with hepatic impairment
Limited data are available on the use of oral ITRACONAZOLE in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population.
Patients with renal impairment
Limited data are available on the use of oral ITRACONAZOLE in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population.
For maximum drug absorption ITRACONAZOLE should be taken immediately following a meal.
Capsules must be swallowed whole with a small amount of water.
Mode of Administration: For oral use only.

4.3 Contraindications:
• Hypersensitivity to the active substance.
•Co-administration of the following drugs is contraindicated with ITRACONAZOLE capsules
- CYP3A4 metabolized substrates that can prolong the QT-interval e.g., astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with ITRACONAZOLE capsules. 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 metabolized HMG-CoA reductase inhibitors such as atorvastatin, lovastatin and simvastatin
- Triazolam and oral midazolam
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)
- Eletriptan
- Nisoldipine
•ITRACONAZOLE 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.
• ITRACONAZOLE capsules must not be used during pregnancy (except for life-threatening cases).
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.

4.5 Interaction with other medicinal products and other forms of Interaction
Drugs affecting the absorption of ITRACONAZOLE
Drugs that reduce the gastric acidity impair the absorption of ITRACONAZOLE from ITRACONAZOLE 100mg Capsules, hard.
Drugs 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, Hypericum perforatum (St John's Wort), 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.
Effects of ITRACONAZOLE on the metabolism of other drugs
ITRACONAZOLE can inhibit the metabolism of drugs 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. This should be taken into account when the inhibitory effect of ITRACONAZOLE on co-medicated drugs is considered.

4.6 Pregnancy and Lactation:
ITRACONAZOLE hard must not be used during pregnancy except for life-threatening cases where the potential benefits to the mother outweighs the potential harm to the foetus.
In animal studies ITRACONAZOLE has shown reproduction toxicity.
There is limited information on the use of ITRACONAZOLE 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 causal 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 candidosis – did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.
Women of childbearing potential
Women of childbearing potential taking ITRACONAZOLE 100mg Capsules, hard should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of ITRACONAZOLE, hard therapy.
Breastfeeding
A very small amount of ITRACONAZOLE is excreted in human milk.
The expected benefits of ITRACONAZOLE capsules therapy should therefore be weighed against the potential risk of breast-feeding. In case of doubt, the patient should not breast-feed
4.7 Effects on ability to drive and use machines
INTRAZ has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse Drug Reactions: Blood and lymphatic system disorders
Leukopenia, Neutropenia, Thrombocytopenia
Immune system disorders: Hypersensitivity
Anaphylactic Reaction, Anaphylactoid Reaction, Angioneurotic Oedema, Serum Sickness
Metabolism and nutrition disorders
Hypokalemia; Hypertriglyceridemia
Nervous system disorders: Headache, Dizziness, Paraesthesia, Hypoaesthesia

4.9 Overdose

No data are available.
In the event of an overdose, 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 hemodialysis.
No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotic for systemic use, triazole derivative.
ATC code: J02A C02
Mechanism of action: ITRACONAZOLE inhibits fungal 14α-demethylase because of its ability to inhibit cytochrome P450,3A4eC-3, resulting in a depletion of ergo sterol is an essential component fungal cell membrane, inhibit of its synthesis result in cellular permeability causing leakage of cellular content and disruption of membrane synthesis by fungi.
It has been used against histoplasmosis, blastomycosis, Cryptococcal meningitis & aspergillosis.
It is broad spectrum Antifungal Activity.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics: The pharmacokinetics of ITRACONAZOLE has been investigated in healthy subjects, special populations and patients after single and multiple dosing. In general, ITRACONAZOLE is rapidly absorbed. Peak plasma concentrations are reached within 2 to 5 hours after oral administration. ITRACONAZOLE is extensively metabolised by the liver into a large number of metabolites. The main metabolite is hydroxy-ITRACONAZOLE, with plasma concentrations about twice those of unchanged ITRACONAZOLE. The mean elimination half-life of ITRACONAZOLE is about 17 hours after a single dose and increases to 34-42 hours after repeated dosing. ITRACONAZOLE has non-linear pharmacokinetics, and consequently ITRACONAZOLE accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with Cmax and AUC values 4 to 7-fold higher than those seen after a single dose. Plasma levels are undetectable 7 days after suspending ITRACONAZOLE treatment. ITRACONAZOLE clearance decreases at higher doses due to saturable hepatic metabolism. ITRACONAZOLE is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with feces.
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 dose. The observed absolute bioavailability of ITRACONAZOLE is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.
T_{max}: 1.5- 4 hours, C_{max}: 10mcg/ml, V_d: 10.7 L/kg, Total clearance : 3.8 ml /min/ kg
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. Brain to plasma ratios were about 1 as measured in beagle dogs. The uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma.

Biotransformation: ITRACONAZOLE is extensively metabolised by the liver into a large number of metabolites. One of the main metabolites is hydroxy-ITRACONAZOLE, which has in vitro antifungal activity comparable to ITRACONAZOLE. Plasma concentrations of the hydroxy-ITRACONAZOLE are about twice those of ITRACONAZOLE. As shown in in vitro studies, CYP 3A4 is the major enzyme that is involved in the metabolism of ITRACONAZOLE.

Elimination: ITRACONAZOLE is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with feces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas fecal excretion of unchanged drug varies between 3 – 18% of the dose. ITRACONAZOLE clearance decreases at higher doses due to saturable hepatic metabolism.

ITRACONAZOLE absorption by keratinous tissue, especially skin, is four times that of plasma and ITRACONAZOLE elimination is related to skin regeneration. Whereas plasma levels are undetectable 7 days after suspending ITRACONAZOLE treatment, in skin therapeutic levels of the drug can be found for 2-4 weeks following the four-week course of treatment. Levels of ITRACONAZOLE were found in the nail keratin one week after start of treatment, persisting for a period of at least six months following a three-month treatment.

Hepatic impairment: A pharmacokinetic study using a single 100 mg dose of ITRACONAZOLE (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC∞ were seen between these two groups. A statistically significant reduction in average Cmax (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.

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. Caution should be exercised when the drug is administered in this patient population.

5.3 Preclinical safety data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sr. No.	Ingredients	Specification
1.	Non Pareil Seeds 20#24	IHS
2.	Hard Gelatin Capsule Shells Size '0' Scarlet/Scarlet	IHS

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store below 30°C. Protect from moisture.

6.5 Nature and contents of container

1 Capsules in Alu /PVDC Blister & 4 such Blister in a carton = 1 x 4's = 4 Capsules.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Ochoa Laboratories
430, Mzz. F, Gundecha Indl. Complex
Akurli Road, kandivali (E).
Mumbai – 400101. India.
E-mail: maheshshah@aurochemgroup.com

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT