Itraconazole

DIGICON ®

Composition:

Itraconazole 100 mg

MOLECULAR INTRODUCTION

Itraconazole is a triazole medicine used to treat fungal infections. It is effective against a broad spectrum of fungi including:

- Dermatophytes (tinea infections)
- Yeasts such as candida and malassezia infections
- Systemic fungal infections such as histoplasma, aspergillus, coccidiodomycosis, chromoblastomycosis

It is sometimes used for inflammatory skin diseases such as atopic eczema, seborrhoeic dermatitis or psoriasis, if a fungus or yeast is thought to be contributing to the condition.

The medication is better absorbed orally when it is taken with a fatty meal or acidic drink (e.g. orange juice). It is bound to proteins such as albumin in the circulating blood and becomes concentrated in fat cells and within skin and nails. It takes one to three days for half of the medication to be cleared from the blood stream. The rest is eliminated in faeces and urine after conversion by the liver into inactive compounds.

Skin concentrations may be 3 to 10-fold higher than those in the blood. It may persist in the skin for up to 4 weeks after the drug has been discontinued and in the nails for up to a year.

PHARMACODYNAMICS:

Itraconazole is an imidazole/triazole type antifungal agent. Itraconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 α-demethylation via the inhibition of the enzyme cytochrome P450 14α-demethylase. This enzyme converts lanosterol to ergosterol, and is required in fungal cell wall synthesis. The subsequent loss of normal sterols correlates with the accumulation of 14 α-methyl sterols in fungi and may be partly responsible for the fungistatic activity of fluconazole. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. Itraconazole exhibits *in vitro* activity against*Cryptococcus neoformans* and *Candida spp.* Fungistatic activity has also been demonstrated in normal and immunocompromised animal models for systemic and intracranial fungal infections due to *Cryptococcus neoformans* and for systemic infections due to *Candida albicans*.

MECHANISM OF ACTION:

Itraconazole interacts with 14-α demethylase, a cytochrome P-450 enzyme necessary to convert lanosterol to ergosterol. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in increased cellular permeability causing leakage of cellular contents. Itraconazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeasts to mycelial forms, inhibit purine uptake, and impair triglyceride and/or phospholipid biosynthesis.

INDICATIONS:

- Vulvovaginal candidiasis,

- Oral candidiasis

- Dermatomycoses,

- 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

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.

DOSAGE REGIMEN:

Route of administration: Oral use.

For maximum drug absorption itraconazole should be taken immediately following a meal.

Capsules must be swallowed whole.

INDICATIONS	**DOSE**	**DURATION OF TREATMENT**
Gynecological infections: - Vulvovaginal candidosis	 200 mg b.i.d. or 200 mg q.d.	 1 day 3 days
Dematological/ophthalmic indications: - Pityriasis versicolor	 200 mg q.d.	 7 days
- Dermatomycoses	200 mg q.d. or 100 mg q.d.	7 days or 15 days[1]
- Oral candidiasis	100 mg q.d.	15 days[2]

[1] for infections in areas that are highly keratinized, such as plantar *Tinea pedis* (fungal foot infection) and palmar *Tineamanus* (fungal infections of the palm), patients must take 200mg b.i.d. for 7 days, or 100mg once a day for 30 days.

[2] in some patients with compromised immune systems, such as neutropenic, AIDS or transplant patients, the bioavailability of oral itraconazole may be diminished. In these cases the dose may have to be doubled.

<u>Onychomycoses</u>

Onychomycoses can be treated using a pulse or a continuous regime.

- *Pulse treatment* (see table below):

Pulse itraconazole treatment consists of taking two capsules twice a day (200mg b.i.d.) for one week.

For fingernail infections two pulse treatments are recommended, and for toenail infections, three. Each pulse should be separated by a period of three weeks with no treatment. Clinical response can be seen by in the form of nail growth when the treatment is ended.

Location of onychomycoses	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Toenails with or without fingernail involvement	First pulse cycle	No itraconazole therapy			Second pulse cycle	No itraconazole therapy			Third pulse cycle
Finger nails only	First pulse cycle	No itraconazole therapy			Second pulse cycle				

- *Continuous treatment:*

Two capsules a day (200mg q.d.) for three months.

The rate of elimination of itraconazole in skin and nail tissue is slower than in blood plasma. Optimum clinical and mycological response is reached two to four weeks after treatment for skin infections, and six to nine months after treatment for nail infections.

Systemic mycoses (doses vary depending on the infecting organism)

The length of treatment for systemic fungal infections should be dictated by the mycological and clinical response to therapy:

INDICATIONS	**DOSE**	**AVERAGE DURATION**	**COMMENTS**
Aspergillosis	200mg q.d.	2-5 months	Increase dose to 200mg b.i.d. in the case of widespread infection
Candidiasis	100-200mg q.d.	3 weeks-7 months	
Non-meningeal cryptococcosis	200mg q.d.	10 weeks	Maintenance therapy (meningeal cases): 200mg q.d.
Cryptococcal meningitis	200mg b.i.d.	2 months – 6 months	
Histoplasmosis	200mg q.d.	8 months	
	200mg b.i.d.		

- Decreased gastric acidity:

Absorption of itraconazole is impaired when gastric acidity is decreased. For information on patients with achlorhydria and patients on acid secretion suppressors or taking acid neutralising medicinal products, (see section 4.4).

Impaired absorption in AIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. In such cases, blood level monitoring and if necessary dose adjustment might be indicated.

Use in children

Itraconazole should not be administered to children as there is limited clinical data describing the paediatric use of this drug (see section 4.3).

Use in elderly patients

Not recommended

Use in 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. (see section 5.2)

Use in 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.

SIDE EFFECTS:

Itraconazole appears to be a relatively safe drug. Side effects, usually minor, are more likely during a prolonged course of treatment.

- Nausea and vomiting (5%)
- Constipation
- Headache
- Dizziness
- Abnormal liver function tests (up to 5% for those on long term therapy, 2% for pulse therapy); significant liver disease is rare

- Allergic skin rash including urticaria
- Endocrine effects including enlarged breasts (in males) and adrenal suppression
- Tingling in the fingers and toes (very rare)
- Congestive heart failure: itraconazole should be used with caution in those with heart problems.

Itraconazole should **not** normally be taken in pregnancy. Although only excreted in tiny amounts from breast milk, it should only be taken by a breast-feeding mother if essential.

CONTRAINDICATION:

Itraconazole 100mg Capsules, hard is contraindicated in patients with a known hypersensitivity to itraconazole or any of the excipients.

Itraconazole must not be used during pregnancy and lactation; with the exception of life-threatening conditions.

Children: there is limited experience with itraconazole in pediatric patients; therefore itraconazole should not be administered to children unless the expected benefits outweigh the risks (see section 4.2).

Coadministration of the following drugs is contraindicated with Itraconazole 100mg Capsules, hard:

- CYP3A4 metabolised 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 100mg Capsules, hard. 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 atorvastatin, lovastatin and simvastatin.

- Triazolam and oral midazolam.

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

- Eletriptan.

- Nisoldipine.

- Itraconazole 100mg Capsules, hard 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.

STORAGE:
Store it in cool, dark place and out of reach of children.

Presentation

10 CAPSULES X 5 BLISTERS

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