Fungicos® (Capsules)

Itraconazole

Antimycotics for systemic use

20100
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FUNGICOS® CAPSULES

PRESENTATION:
Fungicos® Capsules: White to off-white & cream coloured spherical pellets filled in WHITE/ BLUE colored hard gelatin capsule, plain on body and cap. Each hard gelatin capsule contains: Itraconazole 100 mg.

CLINICAL PHARMACOLOGY:
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 $\leq$0.125; susceptible, dose-dependent 0.25-0.5 and resistant $\geq$ 1μg/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 $\leq$ 1 μg/ml. These include:dermatophytes (Trichophyton spp., Microsporum spp., Epidermophyton floccosum); yeasts (Candida spp., including C. albicans, C. tropicalis, C. parapsilosis and C. krusei, Cryptococcus neoformans, Malassezia spp., Trichosporon spp., Geotrichum spp.); Aspergillus spp.; Histoplasma spp., including H. capsulatum; Paracoccidioides brasiliensis; Sporothrix schenckii; Fonsecaea spp.; Cladosporium spp.; Blastomyces dermatitidis; Coccidiodes immitis; Pseudallescheria boydii; Penicillium marneffei; and various other yeasts and fungi.

Pharmacokinetics:
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 capsule dose. The observed absolute bioavailability of Itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.
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, and the uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.
Metabolism:
Itraconazole is extensively metabolised by the liver into a large number of metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of Itraconazole. The main metabolite is hydroxy-itraconazole, which has in vitro antifungal activity comparable to Itraconazole; plasma concentrations of the hydroxy-itraconazole are about twice those of Itraconazole.
Excretion:
Itraconazole is excreted mainly as inactive metabolites in urine (35%) and faeces (54%) within one week of an oral solution dose. Renal excretion of Itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, faecal excretion of unchanged drug varies between 3 – 18% of the dose.

USES:
1. Vulvovaginal candidosis.
2. Pityriasis versicolor.
3. Dermatophytoses caused by organisms susceptible to itraconazole (Trichophyton spp., Microsporum spp., Epidermophyton floccosum) e.g. tinea pedis, tinea cruris, tinea corporis, tinea manuum.
4. Oropharyngeal candidosis.
5. Onychomycosis caused by dermatophytes and/or yeasts.
6. The treatment of histoplasmosis.
7. Fungicos is indicated in the following systemic fungal conditions when first-line systemic anti-fungal therapy is inappropriate or has proved ineffective. This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity.
    - Treatment of aspergillosis and candidosis
    - Treatment of cryptococcosis (including cryptococcal meningitis): in immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system.
    - Maintenance therapy in AIDS patients to prevent relapse of underlying fungal infection.

Fungicos® is also indicated in the prevention of fungal infection during prolonged neutropenia when standard therapy is considered inappropriate.

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DOSAGE AND ADMINISTRATION:

Indication	Dose	Remarks
Vulvovaginal candidosis	200 mg twice daily for 1 day or 200 mg once daily for 3 days	
Pityriasis versicolor	200 mg once daily for 7 days	
Tinea corporis, tinea cruris	100 mg once daily for 15 days or 200 mg once daily for 7 days	
Tinea pedis, tinea manuum	100 mg once daily for 30 days	
Oropharyngeal candidosis	100 mg once daily for 15 days	Increase dose to 200 mg once daily for 15 days in AIDS or neutropenic patients because of impaired absorption in these groups.
Onychomycosis *(toenails with or without fingernail involvement)*	Pulse treatment: 200mg twice daily for 7 days.	Continuous treatment: 200 mg once daily for 3 months

CONTRA-INDICATIONS AND WARNINGS:

Co-administration of a number of CYP3A4 substrates is contraindicated with Fungicos® Capsules. Increased plasma concentrations of these drugs, caused by co-administration with Itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. Fungicos® 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. Fungicos® Capsules must not be used during pregnancy except for life-threatening cases.

Warning and Precautions:

Talk to your doctor or pharmacist before taking this medicine: • If you have ever had kidney problems; your dose of Fungicos® capsules may have to be changed • If you have ever had liver problems such as yellow skin (jaundice); your dose of Fungicos® capsules may have to be changed. If after taking this medicine you have a severe lack of appetite, feel sick (nausea), are sick (vomiting), feel unusually tired, get stomach pain, muscle weakness, yellowing of the skin or whites of the eyes, unusually dark urine, pale stools or hair loss, stop taking Fungicos® capsules and tell your doctor straight away • If you have ever had a heart problem including heart failure (also called congestive heart failure or CHF); Fungicos® capsules could make it worse. If after taking this medicine you get any of the following: • shortness of breath • unexpected weight gain • swelling of your legs or tummy • feel unusually tired • wake up short of breath at night.

Adverse Effects:

Common: • Stomach ache, feeling sick (nausea) • Headache rash

Uncommon: • Problems with periods • Sinusitis, runny nose, coughs and colds • Constipation, diarrhoea, wind, being sick (vomiting), indigestion Rare: • Increases in liver function tests (shown by blood tests) • Unexpected passing of urine or need to urinate (pass water) more often • Problems with sight including blurred vision and double vision • Change in taste • Certain blood disorders which may increase the risk of infections • Ringing in your ears • Hearing loss (may be permanent) • Severe upper stomach pain, often with nausea and vomiting (inflammation of the pancreas) • Swelling due to fluid under the skin.

Overdosage:

Symptoms and signs

In general, adverse events reported with overdose have been consistent with those reported for Itraconazole use.

Treatment

In the event of overdose, supportive measures should be employed. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

Interactions:

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of Itraconazole. Itraconazole is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. Potent inhibitors of this enzyme such as ritonavir, indinavir, clarithromycin and erythromycin may increase the bioavailability of itraconazole. Astemizole, bepridil, cisapride, dofetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with Itraconazole 100mg Capsules, Caution should be exercised when co-administering itraconazole with calcium channel blockers due to an increased risk of congestive heart failure whenit is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust dosages.

Pregnancy and Breast-Feeding:

Fungicos® Capsules must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus. A very small amount of Itraconazole is excreted in human milk. The expected benefits of Fungicos® therapy should be weighed against the risks of breast feeding. In case of doubt, the patient should not breast feed.

PHARMACEUTICAL PRECAUTIONS:

Store in a dry place below 30ºC. Protect from light. Keep all medicines out of the reach of children.

LEGAL CATEGORY:

Prescription Only Medicine (POM)

®Regd. TM

COSMOS

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