## 1. Name of the medicinal product

Fungicos 100 mg Capsules

## 2. Qualitative and quantitative composition

Each Hard gelatin capsule contains 100 mg of Itraconazole.

## 3. Pharmaceutical form

Hard gelatin capsule.

## 4. Clinical particulars

### 4.1 Therapeutic indications

- Vulvovaginal candidosis.
- Pityriasis versicolor.
- Dermatophytoses caused by organisms susceptible to itraconazole *(Trichophyton spp.*, *Microsporum spp.*, *Epidermophyton floccosum*) e.g. tinea pedis, tinea cruris, tinea corporis, tinea manuum.
- Oropharyngeal candidosis.
- Onychomycosis caused by dermatophytes and/or yeasts.
- The treatment of histoplasmosis.

### 4.2 Posology and method of administration

It is for oral administration and must be taken immediately after a meal for maximal absorption. The capsules must be swallowed whole.

Treatment schedules in adults for each indication are as follows:

| ***Indication*** | ***Dose*** |
|---|---|
| Vulvovaginal candidosis | 200 mg twice daily for 1 day |
| 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 |
| Onychomycosis (toenails with or without fingernail involvement) | 200 mg once daily for 3 months |

For skin, vulvovaginal and oropharyngeal infections, optimal clinical and mycological effects are reached 1 - 4 weeks after cessation of treatment and for nail infections, 6 - 9 months after the cessation of treatment. This is because elimination of Itraconazole from skin, nails and mucous membranes is slower than from plasma.

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

| ***Indication*** | ***Dose*** |
|---|---|
| Aspergillosis | 200 mg once daily |
| Candidosis | 100-200 mg once daily |
| Non-meningeal Cryptococcosis | 200 mg once daily |
| Cryptococcal meningitis | 200 mg twice daily |
| Histoplasmosis | 200 mg once daily - 200 mg twice daily |
| Maintenance in AIDS | 200 mg once daily |
| Prophylaxis in neutropenia | 200 mg once daily |

**4.3 Contraindications**

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. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. 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.

**Precautions and warnings**

*Cross-hypersensitivity*

There is no information regarding cross hypersensitivity between Itraconazole and other azole antifungal agents. Caution should be used in prescribing Fungicos Capsules to patients with hypersensitivity to other azoles.

*Cardiac effects*

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 Fungicos Capsules has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of Itraconazole.

*Hepatic effects*

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Fungicos Capsules. 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 were observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving Fungicos Capsules 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.

*Renal impairment*

Limited data are available on the use of oral Itraconazole in patients with renal impairment. The exposure of Itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered.

*Patients with AIDS*

In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal or non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

**4.4 Interaction with other medicinal products and other forms of interaction**

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of Itraconazole. Similarly, Itraconazole may modify the pharmacokinetics of other substances that share this metabolic pathway.

Itraconazole is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. When using concomitant medication, it is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust dosages.

**4.5 Fertility, pregnancy and lactation**

*Pregnancy*

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.

In animal studies Itraconazole has shown reproduction toxicity.

There is limited information on the use of Fungicos 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 Fungicos has not been established.Epidemiological data on exposure to Fungicos 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 child bearing potential*

Women of childbearing potential taking Fungicos menstrual period following the end of Fungicos therapy.

*Lactation*

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.

**4.6 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss.

**4.7 Undesirable effects**

| | |
|---|---|
| **Infections and infestations** | |
| *Uncommon* | Sinusitis, Upper respiratory tract infection, Rhinitis |
| **Blood and lymphatic system disorders** | |
| *Rare* | Leukopenia |
| **Immune system disorders** | |

| | |
|---|---|
| *Uncommon* | Hypersensitivity |
| *Rare* | Serum sickness, Angioneurotic oedema, Anaphylactic reaction |
| **Metabolism and nutrition disorders** | |
| *Rare* | Hypertriglyceridaemia |
| **Nervous system disorders** | |
| *Common* | Headache |
| *Rare* | Paraesthesia, Hypoaesthesia, Dysgeusia |
| **Eye disorders** | |
| *Rare* | Visual disturbance (including diplopia and blurred vision) |
| **Ear and labyrinth disorder** | |
| *Rare* | Transient or permanent hearing loss, Tinnitus |
| **Cardiac disorders** | |
| *Rare* | Congestive heart failure |
| **Respiratory, thoracic and mediastinal disorders** | |
| *Rare* | Dyspnoea |
| **Gastrointestinal disorders** | |
| *Common* | Abdominal pain, Nausea |
| *Uncommon* | Diarrhoea, Vomiting, Constipation, Dyspepsia, Flatulence |
| *Rare* | Pancreatitis |
| **Hepatobiliary disorders** | |
| *Uncommon* | Hepatic function abnormal |
| *Rare* | Serious hepatotoxicity (including some cases of fatal acute liver failure),Hyperbilirubinaemia |
| **Skin and subcutaneous tissue disorders** | |
| *Uncommon* | Urticaria, Rash, Pruritus |
| *Rare* | Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity |
| **Renal and urinary disorders** | |

| | |
|---|---|
| *Rare* | Pollakiuria |
| **Reproductive system and breast disorders** | |
| *Uncommon* | Menstrual disorder |
| *Rare* | Erectile dysfunction |

**4.8 Overdose**

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

**5. Pharmacological properties**

**5.1 Pharmacodynamic properties**

*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.

*In vitro* studies demonstrate that Itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually ≤ 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.

*Candida krusei, Candida glabrata* and *Candida tropicalis* are generally the least susceptible Candida species, with some isolates showing unequivocal resistance to itraconazole *in vitro*.

The principal fungus types that are not inhibited by Itraconazole are Zygomycetes (e.g. Rhizopus spp., Rhizomucor spp., Mucor spp. and Absidia spp.), Fusarium spp., *Scedosporium proliferans* and Scopulariopsis spp.

Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14α-demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux.

**5.2 Pharmacokinetic properties**

**Pharmacokinetics of Telmisartan**

*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.

Absorption of Itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., $H_2$-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases. Absorption of Itraconazole under fasted conditions in these subjects is increased when Fungicos Capsules are administered with an acidic beverage (such as a non-diet cola). When Fungicos Capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a $H_2$-receptor antagonist, Itraconazole absorption was comparable to that observed when Fungicos Capsules were administered alone. Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given.

*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; trough 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.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Empty gelatin hard capsules size 0

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in a dry place below 30°C. Protect from light

### 6.5 Nature and contents of container

PVDC/ALU Blister Packing

### 6.6 Special precautions for disposal and other handling

No special requirements for disposal.

## 7 Marketing authorisation holder

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## 8.Marketing authorisation number(s)

## 9. Date of first authorisation/renewal of the authorization

## 10. Date of revision of the text