Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Fungicos 100 mg Capsules

2. Qualitative and quantitative composition
Each Hard gelatin capsule contains 100 mg of Itraconazole.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Hard gelatin capsule.

White To Off White And Cream Coloured Spherical Pellets Filled In White/Blue Gelatin Capsules.

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

Posology

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:

Short-Term Usage

Table 1: Dose recommendation short term usage

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.
Long Term Usage
Dosage recommendations vary according to the infection treated.

Table 2: Dose recommendation long term usage

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

Paediatric population
Since clinical data on the use of itraconazole in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks. Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes.

Elderly
There are inadequate data on itraconazole in elderly for its use to be recommended, unless the potential benefits outweigh the risks.

Hepatic impairment
Itraconazole is predominantly metabolised by the liver. A slight decrease in oral bioavailability in cirrhotic patients has been observed, although this was not of statistical significance. The terminal half-life was significantly increased. The dose should be adapted if necessary. Monitoring of plasma levels may be necessary.

Renal impairment
The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. Dose adjustment may be considered. Monitoring of plasma levels may be necessary. Itraconazole cannot be removed by dialysis. 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.

Method of administration

Itraconazole is for oral administration and must be taken immediately after a meal for maximal absorption.

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.

4.4 Special warnings and precautions for use

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 preexisting 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.

Reduced gastric acidity
Absorption of itraconazole from Itraconazole is impaired when gastric acidity is reduced. In patients also receiving acid neutralising medicines (eg aluminium hydroxide), these should be administered at least 2 hours after the intake of Itraconazole. In patients with achlorhydria such as certain AIDS patients and patients on acid secretion suppressors (eg H2-antagonists, proton pump inhibitors), it is advisable to administer Itraconazole with a cola beverage.

Hearing Loss
Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction, 3.Effect of itraconazole on the metabolism of other drugs). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

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.

4.5 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 capsules (see 4.4 Special warnings and precautions for use).

Drugs affecting the metabolism of itraconazole
Itraconazole is mainly metabolised through 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:
1. 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 (see 5.2 Pharmacokinetic Properties). This should be taken into account when the inhibitory effect of itraconazole on coadministered drugs is considered.

The following drugs are contraindicated with itraconazole:
• Astemizole, bepridil, cisapride, dofetilide, levamethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with Itraconazole since co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsades 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), ergotmaine and methylergometrine
(methylergonovine).
• Eletripian
• Nisoldipine
Caution should be used when co-administering itraconazole with calcium channel blockers due to an increased risk of congestive heart failure. In addition to possible pharmacokinetic interactions involving the drug metabolizing enzyme CYP 3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of intraconazole.
The following drugs should be used with caution, and their plasma concentrations, 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 vinca alkaloids, busulphan, docetaxel and trimetrexate;
- CYP3A4 metabolised calcium channel blockers such as dihydropyridines and verapamil;
- Certain immunosuppressive agents: ciclosporin, tacrolimus, rapamycin (also known as sirolimus);
- Certain CY3A4 metabolised HMG-CoA reductase inhibitors such as atorvastatin;

- Certain glucocorticosteroids such as budesonide, dexamethasone , methylprednisolone and fluticasone;
- Digoxin (via inhibition of P-glycoprotein);
- Others: carbamazepine, cilostazol, buspirone, alfentanil, alprazolam, brotizolam, midazolam IV, disopyramide, eletriptan, fentanyl, halofantrine, rifabutin, repaglinide, ebastine, reboxetine.

2. No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed.
No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.
Effect on protein binding:
In vitro studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide or sulphame

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.6 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 postmarketing 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.

4.7 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.

4.8 Undesirable effects

The table below presents adverse drug reactions by System Organ Class. Within each System Organ Class, the adverse drug reactions are presented by incidence category, using the following convention: Very common (1/10); Common (1/100 to < 1/10); Uncommon (1/1,000 to < 1/100); Rare (1/10,000 to < 1/1,000); Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

Table 3: Adverse drug reactions

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

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 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

Pharmacotherapeutic classification: (Antimycotics for systemic use, triazole derivatives). ATC code: J02A C02

Mechanism of Action

In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. Antimicrobial Activity: Itraconazole exhibits in vitro activity against Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, and Trichophyton species. Resistance: Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated in vitro and from patients receiving prolonged therapy. Itraconazole is not active against Zygomycetes (e.g., Rhizopus spp., Rhizomucor spp., Mucor spp. and Absidia spp.), Fusarium spp., Scedosporium spp. and Scopulariopsis spp.

Cross-resistance

Several in vitro studies have reported that some fungal clinical isolates with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed. Studies (both in vitro and in vivo) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the 14C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against Aspergillus fumigatus infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

Table 4: Commonly susceptible species

Commonly susceptible species
Aspergillus spp.[2]
Blastomyces dermatitidis[1]
Candida albicans
Candida parapsilosis
Cladosporium spp.
Coccidioides immitis[1]
Cryptococcus neoformans
Epidermophyton floccosum
Fonsecaea spp. [1]
Geotrichum spp.
Histoplasma spp.
Malassezia (formerly Pityrosporum) spp.
Microsporum spp.
Paracoccidioides brasiliensis[1]
Penicillium marneffei[1]
Pseudallescheria boydii

Sporothrix schenckii
Trichophyton spp.
Trichosporon spp.
Species for which acquired resistance may be a problem
Candida glabrata[3]
Candida krusei
Candida tropicalis[3]
Inherently resistant organisms
Absidia spp.
Fusarium spp.
Mucor spp.
Rhizomucor spp.
Rhizopus spp.
Scedosporium proliferans
Scopulariopsis spp.

These organisms may be encountered in patients who have returned from travel outside Europe.
Itraconazole-resistant strains of Aspergillus fumigatus have been reported.
Natural intermediate susceptibility.

5.2 Pharmacokinetic properties

Absorption

Itraconazole is rapidly absorbed after administration of the oral solution. Peak plasma concentrations of the unchanged drug are reached within 2.5 hours following an oral dose. The observed absolute bioavailability of itraconazole under fed conditions 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 hydroxymetabolite). 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. The uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma. Metabolism: Itraconazole is extensively metabolised by the liver into a large number of metabolites. The main metabolite is hydroxyitraconazole which has in vitro antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxymetabolite 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.

Excretion

Itraconazole is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with faeces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas faecal excretion of unchanged drug varies between 3-18% of the dose. As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeks after discontinuation of a 4-week treatment and in nail keratin – where itraconazole can be detected as early as 1 week after start of treatment - for at least six months after the end of a 3-month treatment period.

5.3 Preclinical safety data

Nonclinical data on itraconazole revealed no indications for gene toxicity, primary carcinogenicity or impairment of fertility. At high doses, effects were observed in the adrenal cortex, liver and the mononuclear phagocyte system but appear to have a low relevance for the proposed clinical use. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats and mice at high doses. A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

6. Pharmaceutical Particulars

6.1 List of Excipients

Empty hard gelatin capsule

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

2 years

6.4 Special Precautions for storage

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

6.5 Nature and Content of container

PVDC/ALU Blister Packing

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing Authorization Holder

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8. Marketing Authorization Number
CTD10274

9. Date of first authorization/renewal of the authorization
12/09/2023

10. Date of revision of the text
12/05/2025