PACKAGE INSERT

SCHEDULING STATUS:

PROPRIETARY NAME AND DOSAGE FORM:

ADCO-SPOROZOLE CAPSULES

COMPOSITION:

Each capsule contains 100 mg of itraconazole in a microgranule formulation.

Other ingredients include hypromellose, maize starch and poloxamer 188.

Contains sugar: Sucrose 240 mg per capsule.

PHARMACOLOGICAL CLASSIFICATION:

A.20.2.2 Antimicrobial (chemotherapeutic) agents. Fungicides.

PHARMACOLOGICAL ACTION:

Itraconazole is a triazole antifungal agent that inhibits the cytochrome P-450 dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. This impairment of fungal cell membrane synthesis ultimately results in an antifungal effect.

It is active against strains of the following: dermatophytes *(Tricophyton spp., Microsprum spp., Epidermophyton spp.),* yeasts *(Cryptococcus neformans, Candida spp.), Aspergillus spp., Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Malassezia furfur, Paracoccidioides brasiliensis, Sporothrix shenckii.* Itraconazole also has some antiprotozoal activity against *Leishmania spp.*

The oral bioavailability of itraconazole is maximal when it is taken with or immediately after a full meal.

Mean peak plasma concentrations can be reached within 4 hours following an oral dose. Steady-state levels can be reached within 14 days and the plasma concentrations at steady state are as follows: 0,4 ug/ml (100 mg daily dose), 1, 1 ug/ml (200 mg daily) and 2,0 ug/ml (200 mg twice daily).

Itraconazole is highly protein bound (99,8%); only 0,2% circulates as free drug.

Itraconazole is widely distributed but only small amounts diffuse into the CSF. Concentrations attained in keratinous tissue, especially the skin, are up to 5 times higher than in plasma and elimination is related to epidermal regeneration. Therapeutic concentrations of itraconazole remain in the skin for up to 2-4 weeks after discontinuation of a 4-week treatment. Levels in the nail keratin persist for at least 6 months after the end of a 3 month course of therapy.

Itraconazole is also present in sebum, pus and female genital tissues at concentrations several times higher than simultaneous plasma concentrations. Therapeutic levels in vaginal tissue are maintained for another 2 days after discontinuation of a 3-day course with 200 mg daily and for another 3 days after discontinuation of a 1-day course (200 mg twice daily).

Itraconazole is extensively metabolised by the liver into a large number of metabolites, including hydroxyitraconazole, the major metabolite. Hydroxyitraconazole appears in the blood in concentrations almost twice that of unaltered drug. Many fungi are equally susceptible to the parent drug and the hydroxylated metabolite.

3 to 18 % is excreted in the faeces as unchanged drug; less than 1% is excreted in the urine. The elimination half-life following a single 100 mg dose has been reported as 20 hours; the half-life increases to 30 hours with continued administration.

INDICATIONS:

ADCO-SPOROZOLE may be used for:

1. Persistent vulvovaginal candidiasis which does not respond to conventional treatment.

2. Dermatophytoses unresponsive to topical treatment.

3. Fungal keratitis.

4. Onychomycosis, caused by dermatophytes and/or yeasts.

5. Systemic infections including: aspergillosis, blastomycosis, systemic candidiasis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis.

CONTRA-INDICATIONS:

ADCO-SPOROZOLE is contra-indicated in pregnancy. Adequate contraceptive precautions should be taken by women of childbearing potential during therapy and for one menstrual cycle after stopping therapy, as teratogenicity has been shown in laboratory animals.

Co-administration of terfenadine with **ADCO-SPOROZOLE** is contra-indicated. Less frequent cases of serious cardiovascular adverse events including death, ventricular tachycardia and torsade de pointes have been observed in patients taking itraconazole concomitantly with terfenadine due to increased terfenadine concentrations induced by **ADCO-SPOROZOLE.**

Pharmacokinetic data indicate that another oral antifungal, ketoconazole, inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole, which may prolong QT intervals. *In vitro* data suggest that **ADCO-SPOROZOLE,**

when compared to ketoconazole, has a less pronounced effect on the biotransformation system responsible for the metabolism of astemizole. Based on the chemical resemblance of itraconazole and ketoconazole, co-administration of astemizole with **ADCO-SPOROZOLE** is contra-indicated.

Co-administration of cisapride, quinidine, pimozide, CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin or lovastatin, oral triazolam or midazolam with **ADCO-SPOROZOLE** is contraindicated.

ADCO-SPOROZOLE is also contra-indicated in patients who have shown hypersensitivity to itraconazole or its excipients. Caution should be used in prescribing **ADCO-SPOROZOLE** to patients with hypersensitivity to other azoles.

The use of itraconazole has not been systematically studied in children (below 12 years) or the elderly. **ADCO-SPOROZOLE** should not be administered to treat onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure.

WARNINGS and SPECIAL PRECAUTIONS:

ADCO-SPOROZOLE capsules should be avoided in patients with liver disease. Liver function should be monitored if treatment lasts more than 1 month, or promptly if there are symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. If abnormal liver function is detected, treatment should be stopped.

Cases of serious, usually reversible idiosyncratic hepatitis, which may be fatal, have been observed.

Co-administration of terfenadine with **ADCO-SPOROZOLE** is contra-indicated. Less frequent cases of serious cardiovascular adverse events including death, ventricular tachycardia and torsade de pointes have been observed in patients taking itraconazole concomitantly with terfenadine due to increased terfenadine concentrations induced by **ADCO-SPOROZOLE.**

Pharmacokinetic data indicate that another oral antifungal, ketoconazole, inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole, which may prolong QT intervals. In vitro data suggest that **ADCO-SPOROZOLE,** when compared to ketoconazole, has a less pronounced effect on the biotransformation system responsible for the metabolism of astemizole. Based on the chemical resemblance of itraconazole and ketoconazole, co-administration of astemizole with ADCO-SPOROZOLE is contra-indicated.

Patients should be instructed to take **ADCO-SPOROZOLE** capsules with or immediately after a meal (see

"DOSAGE AND DIRECTIONS FOR USE).

Itraconazole has been shown to have a negative inotropic effect and **ADCO-SPOROZOLE** has been associated with reports of congestive heart failure. **ADCO-SPOROZOLE** should not be used in patients with congestive heart failure or with a history of congestive heart failure, unless the benefit clearly outweighs the risk.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of **ADCOSPOROZOLE.**

In this case absorption may be improved by administering **ADCO-SPOROZOLE** capsules with an acidic drink, such as a cola beverage.

The same applies to patients with achlorhydria and patients on acid secretion suppressors (e.g. H2 antagonists, proton pump inhibitors).

In patients also receiving antacids (e.g. aluminium hydroxide), these should be administered at least 2 hours after the intake of **ADCO-SPOROZOLE** capsules.

If neuropathy occurs that may be attributable to **ADCO-SPOROZOLE,** the treatment should be discontinued.

Dose adjustments may be required in some patients with renal insufficiency.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers.

INTERACTIONS:

Enzyme-inducing drugs such as rifampicin, carbamazepine, phenytoin, or phenobarbitone may decrease plasma concentrations of itraconazole.

Concomitant administration of medicines that reduce stomach acidity, such as antimuscarinics, antacids, proton pump inhibitors and histamine H2-receptor antagonists, may reduce the absorption of **ADCOSPOROZOLE.**

ADCO-SPOROZOLE may interfere with medicines metabolised by hepatic microsomal enzymes, especially cytochrome P450 (CYP3A4), hence the warnings that plasma concentrations of astemizole, cisapride, cyclosporin, felodipine, statins such as lovastatin or simvastatin, midazolam, quinidine, terfenadine, triazolam, and warfarin may be increased. Concentrations of HIV-protease inhibitors such as indinavir or ritonavir may also be increased; **ADCO-SPOROZOLE** plasma concentrations may be increased in turn. The effects of digoxin and of vincristine may be increased by **ADCO-SPOROZOLE** but the efficacy of oral contraceptives might be reduced.

There is a risk of cardiac arrythmias if itraconazole is used concomitantly with astemizole, cisapride, or terfenadine and such combinations should be avoided.

PREGNANCY AND LACTATION:

Pregnancy: See 'CONTRA-INDICATIONS'.

Lactation: **ADCO-SPOROZOLE** capsules should not be administered to breastfeeding women.

DOSAGE AND DIRECTIONS FOR USE:

ADCO-SPOROZOLE capsules should be taken with or immediately after meals for optimal absorption.

1. Vulvovaginal candidiasis: 200 mg twice daily for 1 day.

2. Dermatophytoses:

Tinea corporis or *tinea cruris:* 100 mg daily for 15 days, or 200 mg daily for 7 days.

Tinea pedis or *tinea manuum:* 100 mg daily for 30 days, or 200 mg twice daily for 7 days.

3. Fungal keratitis: 200 mg daily for 21 days.

4. Onychomycosis:

Continuous treatment: 200 mg daily for 3 months

Pulse treatment: 200 mg twice daily for 7 days (1 week)= 1 pulse treatment

Fingernail infections = 2 pulse treatments

Toenail infections = 3 pulse treatments

Pulse treatments are always separated by a 21-day (3 week) drug free period. Therefore, for:

Fingernail infections: 200 mg twice daily for 7 days (1 week), followed by 21-day (3 week) drug free period, followed by another 200 mg twice daily for 7 days (1 week).

Toenail infections: 200 mg twice daily for 7 days (1 week), followed by 21 day (3 week) drug free period, followed by another 200 Mg twice daily for 7 days (1 week) and a further 21-day (3 week) drug free period, followed by a final 200 mg twice daily for 7 days (1 week).

Elimination of itraconazole from skin and nail is slower than from plasma. Optimal clinical mycological effects are thus reached 1 to 4 weeks after the cessation of treatment for skin infections and 6 to 9 months after cessation of treatment for nail infections.

5. Systemic infections: 100 mg to 200 mg daily, increased to 200 mg twice daily for invasive or disseminated infections. (see table below)

Life-threatening infections: 200 mg three times daily for the first 3 days as a loading dose.

Dosages that have been used in systemic mycoses:

Indication	Dose	Median duration	Remarks
Aspergillosis	200 mg daily	2-5 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease.
Candidiasis	100 - 200 mg daily	3 weeks- 7 months	

Histoplasmosis (excluding meningeal histoplasmosis)	200 mg daily - 200 mg twice daily (or 400 mg once daily)	8 months	
Sporotrichosis	100 mg daily	3 months	
Paracoccidioido-mycosis	100 mg daily	6 months	
Chromomycosis	100- 200 mg daily	6 months	
Blastomycosis	100 mg daily - 200 mg twice daily (or 400 mg once daily)	6 months	

SIDE EFFECTS:

Endocrine disorders:

Less frequent: Endocrine effects, such as adrenal suppression and menstrual disorders, and peripheral neuropathy have been reported in a few patients usually when high doses were given. If neuropathy occurs, treatment should be discontinued.

Metabolism and nutrition disorders:

Less frequent: Oedema and hypokalaemia have also been associated with prolonged treatment.

Nervous system disorders:

Less frequent: Headache, dizziness.

Gastrointestinal disorders:

Less frequent: Dyspepsia, abdominal pain, nausea, constipation.

Hepatobiliary disorders:

Less frequent: Cases of hepatitis and cholestatic jaundice have been observed, especially in those patients treated for more than one month.

Skin and subcutaneous tissue disorders:

Less frequent: Pruritus, rash, urticaria, angioedema. Cases of Stevens-Johnson syndrome have also been reported. Alopecia has also been associated with prolonged treatment.

Investigations:

Less frequent: An increase in liver enzyme values has occurred in some patients.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of overdosage, supportive measures should be employed. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate. No specific antidote is available.

ADCO-SPOROZOLE cannot be removed by haemodialysis.

IDENTIFICATION:

Hard gelatin capsules, opaque green cap and body containing yellowish-beige spherical microgranules.

PRESENTATION:

Cartons containing one or more aluminium blister strips of 4, 5, 6 or 7 capsules.

STORAGE INSTRUCTIONS:

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

Do not remove the blister from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

37/20.2.2/ 0559

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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