210.00 mm

140.00 mm

Sporizol Capsule

(Itraconazole)

سپوریزول کیپسول

(اٹراکونازول)

COMPOSITION:

Each capsule contains:

Itraconazole (as IR pellets).....100mg

(USP Specifications)

DESCRIPTION:

Itraconazole, sometimes abbreviated ITZ, is an azole antifungal medication used to treat a number of fungal infection. It includes aspergillosis, blastomycosis, coccidiodomycosis, histoplasmosis, and paracoccidioidomycosis.

MECHANISM OF ACTION:

Itraconazole, a triazole derivative, has a broad spectrum of activity. 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.

INDICATIONS:

Sporizol (itraconazole) capsules are indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

- Blastomycosis, pulmonary and extra pulmonary.
- Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and
- Aspergillosis, pulmonary and extra pulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, and serology) should be obtained before therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Sporizol capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:

- Onychomycosis of the toenail, with or without fingernail involvement, due to dermatophytes (tinea unguium), and
- Onychomycosis of the fingernail due to dermatophytes (tinea unguium). Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

DOSAGE AND ADMINISTRATION:

Itraconazole capsules should be taken with a full meal to ensure maximal absorption. It must be swallowed whole.

Treatment of Blastomycosis and Histoplasmosis:

The recommended dose is 200 mg once daily (2 capsules). If there is no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 100-mg increments to a maximum of 400 mg daily. Doses above 200 mg/day should be given in two divided doses.

Treatment of Aspergillosis:

A daily dose of 200 to 400 mg is recommended.

Treatment in Life-Threatening Situations:

In life-threatening situations, a loading dose should be used. Although clinical studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose of 200 mg (2 capsules) three times daily (600 mg/day) be given for the first 3 days of treatment. Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Treatment of Onychomycosis:

Toenails with or without fingernail involvement: The recommended dose is 200 mg (2 capsules) once daily for 12 consecutive weeks.

Treatment of Onychomycosis:

Fingernails only: The recommended dosing regimen is 2 treatment pulses, each consisting of 200 mg (2 capsules) b.i.d. (400 mg/day) for 1 week. The pulses are separated by a 3-week period without Itraconazole

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

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

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. 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., H2-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 capsules are administered with an acidic beverage (such as a non-diet cola). When itraconazole capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H2-receptor antagonist, itraconazole absorption was comparable to that observed when administered alone.

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%). Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabeled dose, faecal excretion of unchanged drug varies between 3 – 18% of the dose.

PRECAUTIONS:

Cross-hypersensitivity

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

Cardiac effects

Itraconazole has been shown to have a negative inotropic effect and Sporizol 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. Sporizol 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. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g. total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other oedematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, Sporizol should be discontinued. Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be exercised when co-administering itraconazole and calcium channel blockers.

Hepatic effects

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Sporizol 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 Sporizol 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.

Reduced gastric acidity

Absorption of itraconazole from Sporizol Capsules is impaired when gastric acidity is reduced. In patients with reduced gastric acidity, whether from disease (e.g. patients with achlorhydria) or from concomitant medication (e.g. patients taking drugs that reduce gastric acidity), it is advisable to administer Sporizol Capsules with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary.

Pediatrics

Clinical data on the use of Sporizol Capsules in paediatric patients is limited. The use of Sporizol Capsules in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.

Elderly

Clinical data on the use of Sporizol Capsules in elderly patients are limited. It is advised to use Sporizol Capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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.

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. The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Immunocompromised patients

In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), the oral bioavailability of Sporizol Capsules may be decreased. Impaired absorption in AIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. The dose should be adjusted based on the clinical response in these patients. Therapeutic blood level monitoring may be necessary.

Patients with immediately life-threatening systemic fungal infections

Due to the pharmacokinetic properties Sporizol Capsules are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

Patients with AIDS

In patients with AIDS who have received treatment for a systemic fungal infection with Sporizol Capsules and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Neuropathy

If neuropathy occurs which may be attributable to Sporizol Capsules, the treatment should be discontinued.

Disorders of Carbohydrate Metabolism

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Cross-resistance

In systemic candidosis, if fluconazole-resistant strains of Candida species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of Sporizol therapy.

Interchangeability

It is not recommended that itraconazole capsules and oral Solution be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given.

Interaction Potential

Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death.

Pregnancy

Sporizol 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.

Women of child bearing potential

Women of childbearing potential taking Sporizol capsules should use contraceptive precautions. Effective contraception should be continued until the next menstrual period following the end of Sporizol therapy.

Lactation

A very small amount of itraconazole is excreted in human milk. The expected benefits of Sporizol therapy should be weighed against the risks of breast feeding. In case of doubt, the patient should not breast feed.

SIDE EFFECTS:

Infections and infestations:
Sinusitis, Upper respiratory tract infection, Rhinitis.

Blood and lymphatic system disorders
Leukopenia.

Immune system disorders
Hypersensitivity. Serum sickness, Angioneurotic edema, anaphylactic reactions.

Metabolism and nutrition disorders
Hypertriglyceridemia.

Nervous system disorders
Paraesthesia, Hypoesthesia, Dysgeusia, headache.

Eye disorders
Visual disturbance (including diplopia and blurred vision)

Ear and labyrinth disorder
Transient or permanent hearing loss, tinnitus.

Cardiac disorders
Congestive heart failure.

Respiratory, thoracic and mediastinal disorders
Dyspnea.

Gastrointestinal disorders
Abdominal pain, Nausea, Diarrhea, Vomiting, Constipation, Dyspepsia, Flatulence, Pancreatitis.

Hepatobiliary disorders
Hepatic function abnormal, Serious hepatotoxicity (including some cases of fatal acute liver failure), Hyperbilirubinemia.

Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalized exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity, Urticaria, Rash, and Pruritus.

Renal and urinary disorders
Pollakiuria.

Reproductive system and breast disorders
Menstrual disorder, erectile dysfunction.

General disorders and administration site conditions
Edema.

Investigations
Blood creatine phosphokinase increased.

DRUG INTERACTIONS:

Itraconazole is mainly metabolised 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.

Drugs that may decrease itraconazole plasma concentrations

Drugs that reduce the gastric acidity (e.g. acid neutralizing medicines such as aluminum hydroxide, or acid secretion suppressors such as H2-receptor antagonists and proton pump inhibitors) impair the absorption of itraconazole from itraconazole capsules. It is recommended that these drugs be used with caution when coadministered with itraconazole capsules:

- It is recommended that itraconazole be administered with an acidic beverage (such as non-diet cola) upon co-treatment with drugs reducing gastric acidity.
- It is recommended that acid neutralising medicines (e.g. aluminum hydroxide) be administered at least 1 hour before or 2 hours after the intake of itraconazole capsules.
- Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Coadministration of itraconazole with potent enzyme inducers of CYP3A4 may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be largely reduced. Examples include:

Antibacterials: isoniazid, rifabutin, rifampicin.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin.
Antivirals: efavirenz, nevirapine.

Therefore, administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these drugs be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Drugs that may increase itraconazole plasma concentrations

Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole. Examples include:

Antibacterials: ciprofloxacin, clarithromycin, erythromycin,
Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir, ritonavir.

It is recommended that these drugs be used with caution when coadministered with itraconazole capsules. It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured.

Drugs that may have their plasma concentrations increased by itraconazole

Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of drugs metabolised by CYP3A4 and can inhibit the drug transport by P-glycoprotein, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. CYP3A4-metabolised drugs known to prolong the QT interval may be contraindicated with itraconazole, since the combination may lead to ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors, the decline in plasma concentrations may be even more gradual. This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

Examples of drugs that may have their plasma concentrations increased by itraconazole presented by drug class with advice regarding coadministration with itraconazole:

Drug Class	Contraindicated	Not Recommended	Use with Caution
Alpha Blockers		tamsulosin	
Analgesics	levacetylmethadol (levomethadyl), methadone	fentanyl	alfentanil, buprenorphine IV and sublingual, oxycodone
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin
Antibacterials		rifabutin	
Anticoagulants and Antiplatelet Drugs		rivaroxaban	coumarins, cilostazol, dabigatran
Anticonvulsants		carbamazepine	
Antidiabetics			repaglinide, saxagliptin
Antihelmintics and Antiprotozoals	halofantrine		praziquantel
Antihistamines	astemizole, mizolastine, terfenadine		ebastine
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)		eletriptan
Antineoplastics	irinotecan	dasatinib, nilotinib, trabectedin	bortezomib, busulphan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, oral midazolam, pimozide, sertindole, triazolam		alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone
Antivirals			maraviroc, indinavir, ritonavir, saquinavir
Beta Blockers			nadolol
Calcium Channel Blockers	bepridil, felodipine, lercanidipine, nisoldipine		other dihydropyridines, including verapamil
Cardiovascular Drugs, Miscellaneous	ivabradine, ranolazine	aliskiren	
Diuretics	eplerenone		
Gastrointestinal Drugs	cisapride,		aprepitant, domperidone
Immunosuppressants		everolimus	budesonide, ciclesonide, ciclosporin, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus
Lipid Regulating Drugs	lovastatin, simvastatin		atorvastatin
Respiratory Drugs		salmeterol	
SSRIs, Tricyclics and Related Antidepressants			reboxetine
Urological Drugs		vardenafil	fesoterodine. imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine
Other	colchicine, in subjects with renal or hepatic impairment	colchicine	alitretinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan

Drugs that may have their plasma concentrations decreased by itraconazole

Coadministration of itraconazole with the NSAID meloxicam may decrease the plasma concentrations of meloxicam. It is recommended that meloxicam be used with caution when coadministered with itraconazole, and its effects or side effects be monitored. It is recommended that the dosage of meloxicam, if coadministered with itraconazole, be adapted if necessary.

CONTRAINDICATIONS:

Itraconazole capsules are contra-indicated in patients with known hypersensitivity to itraconazole or to any of the excipients.

- Coadministration of a number of CYP3A4 substrates is contraindicated with Sporizol Capsules. Increased plasma concentrations of these drugs, caused by coadministration 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.
- Sporizol 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.
- Sporizol Capsules must not be used during pregnancy except for life-threatening cases.
- Women of childbearing potential taking Sporizol Capsules should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Sporizol Capsules therapy.

STORAGE & INSTRUCTIONS:

Store between 15-25°C. Protect from heat, sunlight and moisture. Keep away from the reach of the children.

To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED:

4 capsules.

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.