

Data Sheet

OZOLE

fluconazole

150 mg capsule

Presentation

OZOLE 150 mg is available for oral administration as a size 1 hard gelatin capsule with an opaque blue body and cap containing 150 mg fluconazole. The capsule is printed Ranbaxy on both cap and body.

OZOLE 150 mg capsule is available as a single treatment pack.

Pharmacology

Pharmacodynamics

Fluconazole is a member of the bis-triazole class of antifungal agents. Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14 alpha-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Pharmacokinetics and Metabolism

In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Oral administration is not affected by concomitant food intake. In fasted normal volunteers, peak plasma concentrations occur between 1 and 2 hours post dose with a terminal plasma elimination half-life of approximately 30 hours (range 20 - 50 hours). The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11 - 12%).

Fluconazole has been found to achieve good penetration into all tissues and body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels.

The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicine. About 11% of the dose is excreted in the urine as metabolites. The pharmacokinetics of fluconazole are markedly affected by reduction in renal function, however, no adjustments in single-dose therapy are necessary. There is an inverse relationship between the elimination half-life and creatinine clearance.

The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis.

There are differences in the pharmacokinetics between adults and children, with children after the neonatal period generally having a faster elimination rate and larger volume of distribution than adults.

Microbiology

Fluconazole administered orally or intravenously was active in a variety of animal models of fungal infections using standard laboratory strains of fungi.

Fluconazole exhibits in vitro activity against *Cryptococcus neoformans* and *Candida* spp. Activity has been demonstrated in vivo in normal and immunocompromised animals against infections with *Candida* spp, including systemic candidiasis and in normal animals with *C. neoformans*, including intracranial infections. One case of cross-resistance of *Candida* to fluconazole in a patient (non-HIV) previously treated with ketoconazole has been reported. The efficacy of fluconazole in vivo is greater than would be apparent from in vitro testing against the above-mentioned fungi.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunocompromised mice showed antagonism of the two medicines in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Indications

OZOLE 150 mg Capsule, given orally, is indicated for vaginal candidiasis.

Dosage and Administration

OZOLE 150 mg Capsule is administered orally

Use in Adults

For vaginal candidiasis OZOLE 150 mg should be administered as a single oral dose.

The median time to onset of symptom relief following a 150 mg single oral dose for the treatment of vaginal candidiasis is one day. The range of time to onset of symptom relief is one hour to nine days.

Use in Children

Single dose fluconazole is not recommended for use in children under 18 years of age except under doctor supervision.

Use in Patients with Renal Impairment

Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single dose therapy are necessary in patients with minor to moderate renal impairment.

Contraindications

OZOLE should not be used in patients with known sensitivity to fluconazole; to related azole compounds; or to any of its excipients.

Coadministration of cisapride is contraindicated (See Interactions)

Warnings and Precautions

In rare cases, as with other azoles, anaphylaxis has been reported.

Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. OZOLE 150 mg should not be used again if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see Adverse Reactions).

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of serious cutaneous reactions to many medicines. Fluconazole should not be used again if a rash develops which is attributable to fluconazole.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory (see Adverse Reactions).

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions (see Adverse Reactions).

Use during Pregnancy and Lactation

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Adverse foetal effects have been seen in animals only at high dose levels associated with maternal toxicity.

Fluconazole should not be used in women who are pregnant or in women of childbearing potential unless adequate contraception is employed.

Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

Driving/Use of Machinery

Experience with OZOLE 150 mg indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2 - 7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of Salmonella typhimurium and in the mouse lymphoma system. Cytogenetic studies in vivo and in vitro showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

Adverse Effects

Fluconazole is generally well tolerated.

The most common undesirable effects observed during vaginal candidiasis clinical trials and associated with fluconazole with an incidence > 1% are:

Nervous System Disorders: Headache.

Gastrointestinal Disorders: Nausea, abdominal pain, diarrhoea, dyspepsia. In addition, the uncommon undesirable effects observed during vaginal candidiasis clinical trials associated with fluconazole are:

Dermatological: Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria.

Nervous System Disorders: Dizziness, flushing, dry mouth, vertigo, hyperkinesia, hypertonia, taste perversion.

Gastrointestinal Disorders: Vomiting, anorexia, flatulence, constipation, loose stools.

Metabolic: Thirst.

Psychiatric: Insomnia, nervousness, female sexual dysfunction.

Reproductive: Intermenstrual bleeding, dysmenorrhoea, leucorrhoea, menorrhagia, uterine spasm, vaginal disorder.

Respiratory: Pharyngitis.

Special Senses: Taste perversion, abnormal vision, visual field defect.

Urinary: Polyuria, renal pain.

General: Fatigue, hot flushes, malaise, back pain, herpes simplex, pain, rigors.

The following adverse events have occurred during experience with overall fluconazole use:

Blood and Lymphatic System Disorders: Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Cardiovascular Disorders: QT prolongation, torsades de pointes (see Precautions).

Nervous System Disorders: Seizures.

Immune System Disorders: Anaphylaxis (including face oedema, angioedema, urticaria and pruritus).

Metabolic and Nutritional Disorders: Hypercholesterolaemia, hypertriglyceridaemia and hypokalaemia.

Hepatobiliary Disorders: Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Skin and Subcutaneous Tissue Disorders: Alopecia, exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Interactions

The relevance of the following medicine interactions to single-dose fluconazole is unknown. Patients on other medications should be advised to consult their doctor or pharmacist before starting fluconazole.

Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP 2C and to a lesser extent the CYP 3A isoforms. There are possibilities that other medicines may affect the metabolism of fluconazole and that fluconazole may affect the metabolism of other medicines. In vitro studies conducted in human hepatic microsomes, demonstrate that the extent of inhibition of CYP 3A isoforms is lowest with fluconazole, when compared with ketoconazole and itraconazole.

Azithromycin: An open-label, randomised, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant interaction between fluconazole and azithromycin.

Hydrochlorothiazide: Concomitant oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in normal volunteers resulted in an increase of 41% in C_{max} and an increase of 43% in AUC of fluconazole, compared to fluconazole given alone. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving diuretics, although the prescriber should bear it in mind.

Rifampicin: Administration of a single oral 200 mg dose of fluconazole after chronic rifampicin administration resulted in a 25% decrease in AUC and a 20% shorter half-life of fluconazole in normal volunteers. Depending on clinical circumstances, an increase of the dose of fluconazole should be considered when it is administered with rifampicin.

Cisapride: Cardiac events including torsades de pointes have been reported in patients receiving fluconazole and cisapride concomitantly. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illness. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Coadministration of cisapride is contraindicated in patients receiving fluconazole (see Contraindications).

Cyclosporin: A kinetic study in renal transplant patients found fluconazole 200 mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100 mg daily, fluconazole did not affect cyclosporin levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients, with or without impaired renal function, receiving fluconazole is recommended.

Oral Contraceptives: Three kinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50 mg fluconazole study, while at 200 mg daily the AUC's of ethinyl estradiol and levonorgestrel were increased 40% and 24% respectively. In a 300 mg once weekly fluconazole study, the AUC's of ethinyl estradiol and norethindrone were increased by

24% and 13% respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Oral Hypoglycaemic Agents: The effects of fluconazole on the pharmacokinetics of the sulphonylurea oral hypoglycaemic agents tolbutamide, glipizide and glibenclamide were examined in three placebo-controlled crossover studies in normal volunteers. All subjects received the sulphonylurea alone and following treatment with 100 mg of fluconazole as a single daily oral dose for 7 days. Fluconazole administration resulted in significant increases in C_{max} and AUC of the sulphonylurea. Several subjects in these three studies experienced symptoms consistent with hypoglycaemia. In the glibenclamide study, several volunteers required oral glucose treatment. As fluconazole is a potent inhibitor of CYP2C8 and CYP2C9, it may also interact with other sulphonylureas (eg. glimepiride and gliclazide) and the thiazolidinediones (eg. pioglitazone and rosiglitazone), which are metabolised by these enzymes. When fluconazole and sulphonylureas or thiazolidinediones are co-administered, blood glucose concentrations should be monitored carefully. The possibility of a hypoglycaemic episode should be borne in mind.

Phenytoin: Concomitant administration of oral fluconazole (200 mg) with phenytoin at steady state resulted in an average increase of 75% of phenytoin AUC values in normal volunteers. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended.

Short Acting Benzodiazepines: Studies in human subjects have reported changes in midazolam pharmacokinetics and clinical effects that are dependent on dosage and route of administration. Single doses of fluconazole 150 mg resulted in modest increases in midazolam concentrations and psychomotor effects following oral administration of 10 mg that may not be clinically significant. At doses used to treat systemic mycoses, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects following oral administration of midazolam 7.5 mg, but only modest increases that are not likely to be clinically significant following intravenous infusion of midazolam 0.05 mg/kg. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

Rifabutin: There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

Tacrolimus: There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were coadministered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk of theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and therapy modified appropriately if signs of toxicity develop.

Warfarin: A single dose of warfarin (15 mg) given to normal volunteers, following 14 days of orally administered fluconazole (200 mg) resulted in a 12% increase in the prothrombin time response (area under the prothrombin time-time curve). One of 13 subjects experienced a 2-fold increase in his prothrombin time response. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended.

Zidovudine: The AUC of zidovudine significantly increased (74%) during coadministration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

Gastrointestinal Medicines: In fasted normal volunteers, absorption of orally administered fluconazole does not appear to be affected by agents that increase gastric pH. Single dose administration of fluconazole (100 mg) with cimetidine (400 mg) resulted in a 13% reduction in AUC and 21% reduction in C_{max} of fluconazole. Administration of an antacid containing aluminium and magnesium hydroxides immediately prior to a single dose of fluconazole (100 mg) had no effect on the absorption or elimination of fluconazole.

Physicians should be alert to the potential for interactions with other medicines for which pharmacokinetic interaction studies have not been conducted.

Overdosage

The minimal lethal human dose has not been established. There have been case reports of overdosage with fluconazole and in one case, a 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8,200 mg of fluconazole. The patient was admitted to hospital, and his condition resolved within 48 hours.

In the event of overdosage, symptomatic treatment (with supportive measures and gastric lavage if necessary) should be undertaken.

Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemodialysis session decreases plasma levels by approximately 50%.

Contact the Poisons Information Centre for advice on the management of an overdose.

Pharmaceutical Precautions

Store below 25°C. Shelf-life 36 months

Medicine Classification

Restricted Medicine.

Package Quantities

Capsules 150 mg: Packs of 1 capsule

Further Information

Fluconazole is a bis-triazole: 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol. It is a white to off-white crystalline powder that is sparingly soluble in water and saline. It has a molecular weight of 306.3.

The ingredients present inside OZOLE 150 mg capsules include: lactose monohydrate, maize starch, sodium lauryl sulfate, colloidal anhydrous silica, and magnesium stearate. In addition, the capsules shells contain: gelatin, patent blue (E133) and titanium dioxide (E171). The black colour in the printing ink is black iron oxide (E172).

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