

FLUCON FOR IV INJECTION 2MG/ML

FLUCONAZOLE 2MG/ML

Description

A colourless to slightly yellow clear sterile solution in colorless glass vials.

Composition

Each ml vial contains 2mg of Fluconazole.

Summary of pharmacodynamics and pharmacokinetics

Fluconazole, a member of the triazole class of antifungal agents, is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol.

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbitone sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes.

Fluconazole 50 mg daily, when given for up to 28 days, has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200 - 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg, do not affect its metabolism.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to fluconazole (e.g. *Candida krusei*). Such cases may require alternative antifungal therapy.

Fluconazole's pharmacokinetic properties are similar following its oral or intravenous administration. Orally administered fluconazole is well absorbed, with plasma levels (and systemic bioavailability) being over 90% of the levels achieved following intravenous administration. Absorption by the oral route is not affected by the joint administration of food. Maximum plasma concentrations when fasting are obtained between 0.5 and 1.5 hours post-dose, with a clearance half-life of approximately 30 hours.

Plasma concentrations are proportional to the dose. 90% steady state levels are reached after 4 or 5 days with multiple once daily doses. The administration of a higher dose on the first day, double that of the normal daily dose, raises plasma levels to 90% of the equilibrium status levels by the second day.

The apparent volume of distribution is close to that of total body water. Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels. High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. Binding to plasma proteins is low (11 - 12%).

Clearance is mostly renal, with approximately 80% of the unmodified dose appearing in the urine. The clearance of fluconazole is proportional to creatinine clearance. There is no evidence of circulating metabolites.

Fluconazole's long plasma elimination half-life, makes it possible to administer a single dose in the treatment of genital candidiasis and a daily dose in the treatment of other indications.

Indications

Fluconazole for IV Injection is a triazole antifungal indicated in the treatments of fungal skin infections and for superficial mucosal (oropharyngeal, esophageal or vaginal) candidiasis. Also for systemic infections including coccidioidomycosis, cryptococcosis and systemic candidiasis, also has been tried in chromoblastomycosis, sporotrichosis, histoplasmosis and blastomycosis.

Adverse reactions/side effects

Fluconazole is generally well tolerated.

The most common undesirable effects observed during clinical trials and associated with fluconazole are:
Nervous System Disorders: Headache.

Gastrointestinal Disorders: Abdominal pain, diarrhea, flatulence and nausea.

Hepatobiliary Disorders: Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT and SGPT.

Skin and Subcutaneous Tissue Disorders: Rash.

In some patients, particularly those with serious underlying diseases eg, AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities (see Precautions) have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

In addition, the following undesirable effects have occurred during post-marketing:
Blood and Lymphatic System Disorders: Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

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

Metabolism and Nutrition Disorders: Hypercholesterolemia, hypertriglyceridemia and hypokalemia.

Nervous System Disorders: Dizziness, seizures and taste perversion.

Cardiac Disorders: QT prolongation and torsade de pointes (see Precautions).

Gastrointestinal Disorders: Dyspepsia and vomiting.

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

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

Precautions/warnings

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. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to fluconazole.

Patients have rarely developed exfoliative cutaneous reactions eg, Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many drugs. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this agent should be

discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.

The co-administration of fluconazole at doses <400 mg/day with terfenadine should be carefully monitored (see Interactions).

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

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

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

Effects on the Ability to Drive or Operate Machineries: Experience with fluconazole indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

Contraindications

Fluconazole for IV Injection is contraindicated in patients with known hypersensitivity to fluconazole or to related azole compounds or to any of the inert ingredients of Flucon. Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of ≥ 400 mg/day based upon results of a multiple dose interaction study.

Co-administration of cisapride and pimozide is contraindicated in patients receiving fluconazole.

Fluconazole is generally inadvised in association with halofantrine.

Fluconazole should not be administered in pregnancy and lactation (see Use in pregnancy & lactation under Precautions).

Dosage and directions for use

Fluconazole for IV Injection may be administered by intravenous.

Intravenous infusion is given as a solution containing 2 mg/mL at a rate of 5 to 10 mL per minute (300 to 600 mL/hour).

For systemic candidiasis, cryptococcal meningitis and other cryptococcal infections, the initial dose is 400 mg followed by 200 to 400 mg daily. Fluconazole may also be used in daily doses of 100 to 200 mg to prevent relapse following primary course of antifungal treatment for acute cryptococcal meningitis in patients with AIDS. For immunocompromised patients at risk of fungal infections, it may be given prophylactically by intravenous infusion in a dose of 50 to 400 mg, for children 3 to 12 mg/kg daily may be given.

For children over 4 weeks of age are 3 mg/kg daily for superficial infections (loading dose of 6mg/kg) and 6 to 12 mg/kg daily for systemic infections. For infants under 2 weeks of age, all doses should be given once every 72 hours; for those aged between 2 to 4 weeks, doses should be given every 48 hours. A maximum dose of 400 mg daily should not be exceeded in children or 12 mg/kg for infants.

Incompatibility

While no specific incompatibilities have been observed, Fluconazole Intravenous Infusion should preferably not be mixed with other drugs before infusion.

Use in pregnancy and lactation

Use during pregnancy: Pregnancy categories C. 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 three or more months with high dose (400 - 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear. Accordingly, use in pregnancy should be avoided, except in patients with severe or potentially life-threatening fungal infections, in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the foetus. Fluconazole should not be used in women of childbearing potential, unless adequate contraception is employed.

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

Drug interactions

The following drug interactions relate to the use of multiple-dose fluconazole; their relevance to single-dose fluconazole has not yet been established.

Anticoagulants: In an interaction study, fluconazole increased the prothrombin time (12 %) after warfarin administration in healthy males. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria and melaena) have been reported in association with increases in prothrombin time, in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored.

Benzodiazepines (short acting): Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole, than with fluconazole administered intravenously. 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.

Endogenous steroids: Fluconazole 50 mg daily does not affect endogenous steroid levels in females: 200 - 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

Sulphonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be given jointly to diabetic patients, although the possibility of a hypoglycaemic episode must be considered. Blood glucose levels must therefore be monitored and the dose of sulphonylurea adjusted accordingly.

Hydrochlorothiazide: In a pharmacokinetic interaction study, the co-administration of multiple doses of hydrochlorothiazide in healthy volunteers receiving fluconazole, increased the plasma concentrations of fluconazole by 40 %. An effect of this magnitude should not require any change in the dosage regimen of fluconazole in patients simultaneously receiving diuretics, although this should be taken into consideration by the prescriber.

Phenytoin: The concomitant administration of fluconazole and phenytoin may increase levels of phenytoin to a clinically significant degree. If both drugs need to be given concomitantly, levels of phenytoin must be monitored and the dose of phenytoin adjusted to maintain therapeutic levels.

Oral contraceptives: Two pharmacokinetic studies were conducted with combined oral contraceptives and multiple fluconazole doses. In the study using 50 mg fluconazole, there were no relevant effects on hormone level. However, using 200 mg fluconazole daily, the area under the curve (AUC) for ethinylestradiol and levonorgestrel, increased by 40 % and 24 % respectively. Thus, multiple dose use of fluconazole at these levels is unlikely to affect the efficacy of combined oral contraceptives.

Rifampicin: The concomitant administration of fluconazole and rifampicin gave rise to a 25 % reduction in the AUC and a 20 % shorter half-life of fluconazole. Thus, an increase in the dose of fluconazole should be considered for patients receiving concomitant rifampicin.

Cyclosporin: A pharmacokinetic study conducted on kidney transplant patients, showed that a daily dose of 200 mg fluconazole slowly increased the concentrations of cyclosporin. However, another multiple-dose study using 100 mg fluconazole daily, showed that levels of cyclosporin were not affected in patients following bone marrow transplants. Thus, the monitoring of the plasma concentration of cyclosporin is recommended in patients taking fluconazole.

Theophylline: In a placebo-controlled interaction study, the administration of 200 mg fluconazole daily for 14 days, led to a reduction of 18% in the mean plasma clearance figure of theophylline. Therefore, patients receiving high doses of theophylline or patients with high risk of theophylline toxicity, should be carefully monitored for signs of theophylline toxicity when receiving fluconazole. Treatment should be appropriately modified if signs of toxicity develop.

Terfenadine: Due to the occurrence of serious dysrhythmias (secondary to prolongation of the QTc interval), in patients receiving other azole antifungals in conjunction with terfenadine, interaction studies have been performed. In one study, a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. In another study, a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole, taken in multiple doses of 400 mg per day or greater, significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness and chest pain in patients taking concomitant fluconazole and terfenadine, where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine should not be taken in combination with fluconazole.

Cisapride: There have been reports of cardiac events including torsades de pointes, in patients to whom fluconazole and cisapride were co-administered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illnesses and the relationship of the reported events to a possible fluconazole-cisapride drug interaction is unclear. There have been no formal drug interaction studies with fluconazole and cisapride. Because of the potential seriousness of such an interaction, it is recommended that cisapride is not taken in combination with fluconazole.

Zidovudine: Two pharmacokinetic studies have shown increases in levels of zidovudine, caused very probably by the fall in the conversion of zidovudine to its main metabolite. One study determined the levels of zidovudine in AIDS or ARC patients, before and after the daily administration of 200 mg fluconazole for 15 days. A significant increase was observed in the zidovudine AUC (20%). A second randomised two-period, two-treatment crossover study, examined the levels of zidovudine in patients infected with HIV. On two occasions, with an interval of 21 days, patients received 200 mg zidovudine every 8 hours, either with or without 400 mg of fluconazole daily, for 7 days. The AUC of zidovudine increased significantly (74%) during joint administration with fluconazole. Therefore, patients receiving this combination should be monitored for the appearance of adverse reactions related to zidovudine.

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 also been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. 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 also been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were co-administered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

The use of fluconazole in patients concurrently taking astemizole or other drugs metabolised by the cytochrome P450 system, may be associated with elevations in serum levels of these drugs. In the absence

of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.

While no interaction studies have been conducted with other drugs, the possible appearance of other pharmacological interactions is not ruled out.

Overdosage, symptoms and treatment

There has been a reported case of overdosage with fluconazole. A 42 year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behavior after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to the hospital, and his condition resolved within 48 hrs.

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

Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A 3-hr hemodialysis session decreases plasma levels by approximately 50%.

Presentation

This injection is available in 50ml vials

One vial are packed into one paper box.

Storage conditions

Protect from light and store below 30°Celsius. Keep out of reach of children.

Shelf-life

The injections can be used within 36 months from the date of manufacture if kept as recommended.

Discard any unused portion.

Registration number

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