AVEZOL CAPSULE 150MG

AVEX

Composition

Fluconazole 150mg per capsule

Description

Turquoise, hard gelatine capsule, size 1, containing white to off-white powder.

Pharmacodynamic

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.

Pharmacokinetic

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steadystate levels are reached by day 4-5 with multiple once daily dosing.

Administration of loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

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, epidemisdermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentration was still 5.8 microgram/g.

The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

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

A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a capsule or in an oral suspension by rinsing and retaining in mouth for 2 minutes and swallowing. The maximum concentration of fluconazole in saliva after the suspension was observed 5 minutes after ingestion, and was 182 times higher than the maximum saliva concentration after the capsule which occurred 4 hours after ingestion. After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

Indication

Avezol is indicated for the treatment of the following conditions:

Genital candidiasis, Vaginal candidiasis, acute or recurrent. Candidal balanitis. The treatment of partners who present with symptomatic genital candidiasis should be considered.

Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor, and dermal candida infections.

Recommended Dose

In adults Vaginal candidiasis or candidal balanitis - 150mg single oral dose.

For dermal infections including tinea pedis, corporis, cruris and candida infections the recommended dosage is 150mg once weekly.

Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks.

For tinea versicolor, the recommended dose is 300 mg once weekly for 2 weeks; a third weekly dose of 300 mg may be needed in some patients, whereas, in some patients, a single dose of 300-400 mg may be sufficient.

In children Despite extensive data supporting the use of Avezol in children there are limited data available on the use of Avezol for genital candidiasis in children below 16 years. Use at present is not recommended unless antifungal treatment is imperative and no suitable alternative agent exists.

Use in elderly The normal adult dose should be used.

Use in renal impairment Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required.

Contraindications

Avezol should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any other ingredient in the formulation.

Co-administration of terfenadine or cisapride is contra-indicated in patients receiving Avezol.

Warnings and precautions

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in haematological, hepatic, renal and other biochemical function test results have been observed during treatment with Avezol but the clinical significance and relationship to treatment is uncertain.

Very rarely, patients who died with severe underlying disease and who had received multiple doses of Avezol had post-mortem findings which included hepatic necrosis. These patients were receiving multiple concomitant medications, some known to be potentially hepatotoxic, and/or had underlying diseases which could have caused the hepatic necrosis.

In cases of hepatotoxicity, no obvious relationship to total daily dose of Avezol, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of Avezol therapy.

As a causal relationship with Avezol cannot be excluded, patients who develope abnormal liver function tests during Avezol therapy should be monitored for the development of more serious hepatic injury. Avezol should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with Avezol.

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 severe cutaneous reactions to many drugs.

If a rash develops in a patient which is considered attributable to Avezol, further therapy with this agent is not recommended.

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

Some azoles, including fluconazole, have been associated wih prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. Although the association of Fluconazole and QT-prolongation has not been fully established, fluconazole should be used with caution in patients with potentially proarrythmic conditions such as:

- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrythmias
- Concomitant medication not metabolized by CY34A but known to prolong QT interval
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalaemia.

Interactions

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose Avezol has not yet been established:

Rifampicin Concomitant administration of Avezol and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life, of fluconazole. In patients receiving concomitant rifampicin, an increase in the Avezol dose should be considered.

Hydrochlorothiazide In a kinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving Avezol increased plasma concentrations of fluconazole by 40%. An effect of this magniture should not necessitate a change in the Avezol dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.

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 melena) 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.

Sulphonylureas Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenchlamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind.

Phenytoin Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinically significant degree. If it is necessary to administer both drugs concomitantly, phenytoin levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels.

Oral contraceptives Two kinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50mg fluconazole study, while at 200mg daily the AUCs of ethinyloestradiol and

levonorgestrel were increased 40% and 24% respectively. Thus multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

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

Cyclosporin A kinetic study in renal transplant patients found fluconazole 200mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100mg daily, fluconazole did not affect cyclosporin levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.

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

Terfenadine Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400mg 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 not be taken in combination with fluconazole. (See "Contra-indications").

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. Because of the potential seriousness of such an interaction, co-administration of cisapride is contraindicated in patients receiving fluconazole.

Zidovudine Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, twotreatment cross-over study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200mg every eight hours either with or without fluconazole 400mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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 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 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.

Interaction studies have shown that when oral fluconazole is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Pregnancy and lactation

Use during pregnancy

There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150mg of fluconazole as a single or repeated dose in the first trimester.

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom Avezol may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus.

Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.

There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400mg/day to 800mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 times the recommended human dose) to 320 mg/kg, embryolethality in rats were increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification.

Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high dose (400-800mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

Use during lactation

Fluconazole is found in human breast milk at concentrations similar to plasma. Breast-feeding may be maintained after a single dose of 150mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole.

Effects on ability to drive and use machines

Experience with Avezol indicates that therapy is unlikely to impair a patient's ability to drive or use machinery

Undesirable effects

Fluconazole is generally well tolerated. The most common undesirable effects observed during clinical trials and associated with fluconazole are:

Central and Peripheral Nervous System: Headache.

Skin/Appendages: Rash.

Gastrointestinal: Abdominal pain, diarrhoea, flatulence, nausea.

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

Liver/Biliary: Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

In addition, the following undesirable effects have occurred during post-marketing:

Central and Peripheral Nervous System: Dizziness, seizures.

Skin/Appendages: Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrosis.

Gastrointestinal: Dyspepsia, vomiting.

Haematopoietic and Lymphatic: Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Body As A Whole

Allergic reaction: Anaphylaxis (including angioedema, face oedema, pruritus), urticaria.

Liver/Biliary: Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional: Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Other senses: Taste pervesion.

Cardiac Disorders: QT prolongation, torsade de pointes

Overdose

There have been 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 8200mg of fluconazole, unverified by his physician. The patient was admitted to the hospital and his condition resolved within 48 hours.

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

As 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%.

Storage

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

Pack size: Alu/PVC blister of 1 capsule/box

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