FUKOLE® CAPSULE 150MG

Ingredient(s):
Each capsule contains:
Fluconazole …… 150mg

Pharmacodynamics:
Fluconazole, a member of a new class of triazole antifungal agents, is a potent and specific inhibitor of fungal sterol synthesis.

Pharmacokinetics:
Bioavailability: 90% (fasting)
Volume of distribution: 0.7-1L/kg
Protein binding: 11%
Metabolism: Renal
Half- life: 30 hours(normal renal function)
Time to peak serum concentration: 1-2 hours
Renal excretion: >80% unchanged.

Indication(s):
Treatment and prevention of cryptococcal meningitis and other cryptococcal infections; treatment of vaginal, oropharyngeal and other forms of candidiasis; prevention of fungal infections in immunocompromised patients.

Dosage and Administration:
Adult:
Vaginal candidiasis: 150mg single oral dose
Oropharyngeal candidiasis: 50mg once daily for 7-14 days. Max 14 days except in severely immunocompromised patients.
Atrophic oral candidiasis associated with dentures: 50mg once daily for 14 days concurrently with local antiseptic measures to the dentures.
Other candidal infections of mucosa: 50mg daily for 14-30 days. May be increased to 100mg daily.
Candidaemia, disseminated candidiasis and other invasive candidal infections:
400mg initially followed by 200mg daily. May be increased to 400mg daily.
Cryptococcal meningitis and cryptococcal infections at other sites:
400mg initially then 200-400mg daily for 6-8 weeks.
Prevention of relapse of cryptococcal meningitis in patients with AIDS:
200mg daily after a full course of primary therapy.
Prevention of fungal infections in immunocompromised patients considered at risk as a consequence of HIV infections or neutropenia following cytotoxic chemotherapy, radiotherapy or bone marrow transplant: 50mg/day or 100mg/day.
Tinea pedis: 150mg/wk for 2-6 weeks
Tinea corporis or cruris: 150mg/wk for 2-4 weeks
Pityriasis versicolor: 50mg/day for 2-4 weeks

Route of Administration:
Oral

Contraindication(s):
Patients with known hypersensitivity to fluconazole or to related azole compounds.

Side Effect(s) / Adverse Reaction(s):
Nausea, abdominal pain, diarrhoea, flatulence; rash.

Precaution(s) / Warning(s):
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 attributed 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 <400mg/day with terfenadine should be carefully monitored.
There have been reports of cardiac events including *torsade de pointes* in patients receiving concomitant administration of fluconazole with cisapride. Patients should be carefully monitored if fluconazole is to be co-administered with cisapride.
In rare cases, as with other azoles, anaphylaxis has been reported.

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

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

Mutagenicity:
Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000mcg/mL) showed no evidence of chromosomal mutations.

Impairment of Fertility :
Fluconazole did not affect the fertility of male or female rats treated orally with daily doses 5, 10 or 20 mg/kg or with parenteral doses of 5,25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg orally. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg (approximately 5-15 times the recommended human dose) and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

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 fluconazole 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 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 *coccidiodomycosis* (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 5mg/kg or 10mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossicification were observed at 25mg/kg and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60 times the recommended human dose) to 320mg/kg, embryoletahlity in rats were increased and fetal abnromalities 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.

Drug Interaction(s):
1. Anticoagulants: In an interaction study, fluconazole increased the prothrombin time after warfarin administration in healthy males. Though the magnitude of change was small (12%), careful monitoring of prothrombin time in patients receiving coumarin-type anticoagulants is recommended.
2. 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 co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind.
3. Hydrochlorothiazide: In a kinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.
4. 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.
5. Oral contraceptives: Two 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 50mg fluconazole study, while at 200mg daily, the AUCs of ethinyl estradiol 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.
6. Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.
7. Cyclosporin: A kinetic study in renal transplant patients found fluconazole 200mg daily to slowly increase cyclosporine concentrations. However, in another multiple-dose study with 100mg daily, fluconazole did not affect cyclosporine levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.
8. 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 rate 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 therapy modified appropriately if signs of toxicity develop.
9. Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction 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 400 and 800mg daily dose of fluconazole demonstrated that fluconazole taken in doses of >400mg/day significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of $\geq$400mg with terfenadine is contraindicated. The co-administration of fluconazole at doses < 400mg/day with terfenadine should be carefully monitored.
10. Cisapride: There have been reports of cardiac events including *torsade de pointes* in patients to whom fluconazole and cisapride were coadministered.
11. 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.
12. 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.
13. 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 2nd randomized, 2-period, 2-treatment cross-over study examined zidovudine levels in HIV infected patients. On 2 occasions, 21 days apart, patients received zidovudine 200mg every 8 hrs either with or without fluconazole 400mg daily for 7 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.
14. The use of fluconazole in patients concurrently taking cisapride, asternizole, rifabutin, tacrolimus or other drugs metabolized by the cytochrome P-450 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.
15. 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 clinical significant impairment of fluconazole absorption occurs. Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but such interactions may occur.

Symptoms and Treatment for Overdosage, and Antidote(s):
In the event of overdosage, supportive measures and symptomatic treatment, with gastric lavage if necessary, may be adequate. Fluconazole is largely excreted in the urine; forced diuresis would probably increase the elimination rate. A 3-hr session of haemodialysis decreases plasma levels by approximately 50%.

Shelf-Life:
3 years from the date of manufacture.

Storage Condition(s):
Store at temperature below 30ºC. Protect from light and moisture.

Product Description:
A #1 light blue capsule marked with " YSP / FEC15 " both cap and body, containing white powder.

Dosage Forms and Packaging Available:
Blister pack of 1's and 10's x 50.

Y. S. P. ®
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