Fluzan®

Fluconazole

FORMS AND PRESENTATION
Fluzan®: Tablets: Box of 1.
COMPOSITION:
Fluzan®: Each tablet contains: Fluconazole 150 mg.
Excipients: microcrystalline cellulose, dicalcium phosphate anhydrous, croscarmellose sodium, povidone, magnesium stearate.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
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.
Both orally and intravenously administered Fluconazole was active in a variety of animal fungal infection models. Activity has been demonstrated against opportunistic mycoses, such as infections with *Candida* spp. including systemic candidiasis in immunocompromised animals; with *Cryptococcus neoformans*, including intracranial infections; with *Microsporum* spp. and with *Trichophyton* spp. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitides*; with *Coccidoides immitis*, including intracranial infection and with *Histoplasma capsulatum* in normal and immunosuppressed animals.
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 is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole 50mg daily given 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 200-400mg 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 50mg do not affect its metabolism.
Pharmacokinetic Properties
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 steady-state 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 levels 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 (Cerebrospinal fluid) 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. 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.
Pharmacokinetics in Children
In children, the following pharmacokinetics data have been reported:

Age Studied	Dose (mg/kg)	Half-life (hours)	AUC (microgram.h/ml)
11 days- 11 months	Single-IV 3mg/kg	23	110.1
9 months- 13 years	Single-Oral 2mg/kg	25.0	94.7
9 months- 13 years	Single-Oral 8mg/kg	19.5	362.5
5 years- 15 years	Multiple-IV 2mg/kg	17.4*	67.4
5 years- 15 years	Multiple-IV 4mg/kg	15.2*	139.1
5 years- 15 years	Multiple-IV 8mg/kg	17.6*	196.7
Mean age 7 years	Multiple-Oral 3mg/kg	15.5	41.6

*Denotes final day
In premature new-borns (gestational age around 28 weeks), intravenous administration of Fluconazole of 6mg/kg was given every third day for a maximum of five doses while the premature new-borns remained in the intensive care unit. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13.
The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13.
The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and which increased with time to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.
Preclinical safety data
Reproductive toxicity: Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60x the recommended human dose) to 320mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification.
These effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.
Carcinogenesis: 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. Male rats treated with 5 and 10mg/kg/day had an increased incidence of hepatocellular adenomas.
Mutagenesis: 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 1000µg/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 of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. 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 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 oestrogen-lowering property produced by high doses of Fluconazole. Such a hormone change has not been observed in women treated with Fluconazole.
INDICATIONS
Fluzan® 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.
CONTRAINDICATIONS
Fluconazole should not be used in patients with known hypersensitivity to Fluconazole or to related azole compounds or any other ingredient in the formulation.
Fluconazole should not be co-adminstered with cisapride or terfenadine which are known to both prolong the QT – interval and are metabolised by CYP3A4.
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 Fluconazole 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 Fluconazole 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 Fluconazole, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of Fluconazole therapy.
As a causal relationship with Fluconazole cannot be excluded, 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 during treatment with Fluconazole.
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 Fluconazole, 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 with 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.

PREGNANCY AND LACTATION
Use during pregnancy 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 and these events is unclear. Accordingly, Fluconazole should not be used in pregnancy, or 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, and the relevance to single-dose Fluconazole has not yet been established:
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 in

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the Fluconazole dose should be considered.

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.

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 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. 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, 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.

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.

In a 300 mg once weekly Fluconazole study, the AUCs of ethinyl estradiol and norethindrone were increased by 24% and 13%, respectively.

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.

Cisapride There have been reports of cardiac events including torsades de pointes in patients to whom Fluconazole and cisapride were co-administered. 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. 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 contra-indicated 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 (AIDS-related complex) patients before and following Fluconazole 200mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment 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. This is particularly important for drugs known to prolong QT interval. 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.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but that such interactions may occur.

ADVERSE EFFECTS

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

Nervous System Disorders: Headache.

Skin and Subcutaneous Tissue Disorders: Rash.

Gastrointestinal Disorders: 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.

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

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

Nervous System Disorders: Dizziness, seizures, taste perversion.

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

Gastrointestinal Disorders: Dyspepsia, vomiting.

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

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

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

Metabolism and Nutrition Disorders: Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Cardiac Disorders: QT prolongation, torsade de pointes.

DOSAGE AND ADMINISTRATION

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

In children Despite extensive data supporting the use of Fluzan® in children there are limited data available on the use of Fluzan® 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.

OVERDOSAGE

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 CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: July 2016.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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