PRODUCT INFORMATION

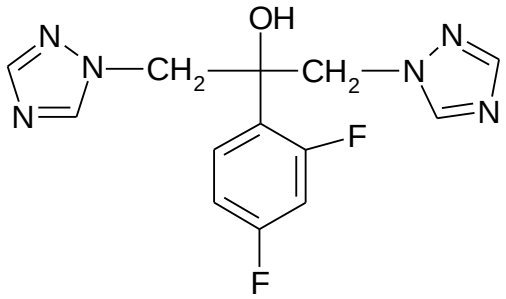
FLUFEME 150mg CAPSULE

NAME OF THE DRUG

Fluconazole

DESCRIPTION

Chemical name: 2-(2,4-difluorophenyl)-1,3-bis (1H-1,2,4-triazol-1-yl) -2-propanol.
Molecular formula: $C_{13}H_{12}F_2N_6O$.



Fluconazole

MW: 306.3. *CAS:* 86386-73-4.

Fluconazole is a white to off-white crystalline powder which is sparingly soluble in water and saline.

Flufeme capsules also contain inactive ingredients:
Lactose, maize starch, magnesium stearate, colloidal anhydrous silica, sodium lauryl sulfate, titanium dioxide, gelatin, Black monogramming ink (107581 or 2328).

PHARMACOLOGY

Pharmacodynamics
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 species. Activity has been demonstrated *in vivo* in normal and immunocompromised animals against infections with Candida sp., including systemic candidiasis, and in normal animals with *Cryptococcus neoformans*, including intracranial infections. One case of cross resistance of Candida to fluconazole in a patient (not infected with human immunodeficiency virus (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 abovementioned fungi.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunocompromised mice showed antagonism of the two drugs in systemic infection

with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Pharmacology. Fluconazole is a member of the bis-triazole class of antifungal agents. Fluconazole is a highly selective inhibitor of fungal cytochrome P450 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. Fluconazole 50mg daily given for up to 28 days has been shown not to affect corticosteroid levels or adrenocorticotrophic hormone (ACTH) stimulated response in healthy female volunteers. Plasma oestradiol levels and urinary free cortisol levels were decreased with little effect on plasma testosterone levels. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50mg do not affect its metabolism.

Pharmacokinetics

Adults. The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. In fasted normal volunteers, peak plasma concentrations occur between one and five hours after the dose with a terminal plasma elimination half-life of approximately 30 hours (range 20 to 50 hours). Plasma concentrations are proportional to dose and steady-state levels are reached within five to ten days with oral doses of 50 to 400 mg once daily. Steady-state levels are approximately 2.5 times the levels achieved with single doses. Administration of a 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 to 12%).

Fluconazole has been found to achieve good penetration into all tissues and body fluids studied. See table below.

Tissue or Fluid	Tissue (fluid): Plasma Concentration*
Cerebrospinal fluid**	0.5 – 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Blister skin	2

* Relative to concurrent concentrations in plasma in subjects with normal renal function
** Independent of degree of meningeal inflammation

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

necessary with single dose fluconazole therapy. A three hour haemodialysis session reduces plasma concentration by about 50%.
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 in adults.

INDICATIONS
Treatment of vaginal candidiasis.

CONTRAINDICATIONS
Known sensitivity to fluconazole, related azole compounds or any of the excipients of Flufeme.

Co-administration of other drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, amiodarone, pimozide and quinidine is contraindicated in patients receiving fluconazole (see PRECAUTIONS: INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

Anaphylaxis has been reported in rare instances.

Fluconazole should be administered with caution to patients with liver dysfunction.
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 hepatoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed.
Fluconazole should not be used again if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see ADVERSE EFFECTS).

Patients have rarely developed exfoliative cutaneous reactions, e.g. 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 drugs. 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 postmarketing 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. Fluconazole should be administered

with caution to patients with these potentially proarrhythmic conditions (see ADVERSE EFFECTS).

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

Fluconazole should be administered with caution to patients with renal dysfunction.

Fluconazole is a potent CYP2C9 and CYP2C19 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole -treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP3A4 should be monitored (See INTERACTIONS WITH OTHER MEDICINES).

Flufeme capsules contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with prednisone is described in INTERACTIONS WITH OTHER MEDICINES.

Carcinogenesis, mutagenesis, 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 two to seven 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 four 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 given orally. 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 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. (See Pharmacology.)

Use in pregnancy. (Category D)
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 fluconazole therapy (400 to 800

mg/day) for coccidiomycosis. 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. These findings are not considered relevant to fluconazole used at therapeutic doses.

A few published case reports describe a distinctive and a rare pattern of birth defects among infants whose mother received high-dose (400-800 mg/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.

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

Use in lactation.
Fluconazole has been found in human breast milk at concentrations similar to those in plasma, hence its use in breastfeeding women is not recommended.

Effects on driving and using machinery

When driving vehicles or operating machinery it should be taken into account that occasionally dizziness or seizures may occur.

INTERACTIONS WITH OTHER MEDICINES

The relevance of the following drug 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 CYP2C and to a lesser extent the CYP3A isoforms. Coadministration of fluconazole with some other drugs metabolized primarily by these P450 isoforms may result in altered plasma concentrations of these medications that could change therapeutic effects and/or adverse event profiles. There are possibilities that other drugs may affect the metabolism of fluconazole and that fluconazole may affect the metabolism of other drugs. *In vitro* studies conducted in human hepatic microsomes demonstrate that the extent of inhibition of CYP3A isoforms is lowest with fluconazole, when compared with ketoconazole and itraconazole.

Clinically or potentially significant drug interactions have been observed between fluconazole and the following agents: short acting benzodiazepines, cisapride, coumarin-type anticoagulants, cyclosporin, hydrochlorothiazide, oral hypoglycaemics, phenytoin, rifampicin, rifabutin, tacrolimus and theophylline. These are described in greater detail below. The drug/drug interactions described below include both interactions mediated through effects on P450 metabolism and interactions mediated through other mechanisms.

Effects of other medicinal products on fluconazole:

The exposure to fluconazole is significantly increased by the concomitant administration of the following agent.

Hydrochlorothiazide.
Concomitant oral administration of Fluconazole 100mg and hydrochlorothiazide 50mg for ten days in normal volunteers resulted in an increase of 41% in Cmax and an increase of 43% in area under the curve (AUC) of fluconazole, compared to fluconazole given alone. Overall the plasma concentrations of fluconazole were approximately 3.26 to 6.52 micromol/L higher with concomitant diuretic. These changes are attributable to a mean net reduction of approximately 20% in renal clearance of fluconazole.

The exposure to fluconazole is significantly decreased by the concomitant administration of the following agent.

Rifampicin.
Administration of a single oral dose of fluconazole 200mg 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.

Minor or no significant pharmacokinetic interactions that require no dosage adjustment:

Gastrointestinal drugs
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 100mg with cimetidine 400mg 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 100mg had no effect on the absorption or elimination of fluconazole.

Effects of fluconazole on other medicinal products:

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 2C19 and a moderate inhibitor of CYP3A4. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 co-administered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.

Alfentanil
A study observed a reduction in clearance and distribution volume as well as prolongation of $t_{1/2}$ of alfentanil following concomitant treatment with fluconazole. A

possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

Amiodarone
Concomitant administration of fluconazole with amiodarone may result in inhibition of amiodarone metabolism. Use of amiodarone has been associated with QT prolongation. Co-administration of fluconazole and amiodarone is contraindicated (see CONTRAINDICATIONS).

Amitriptyline, Nortriptyline
Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericin B
Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small addictive antifungal effect in systemic infection with C.albicans, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two drugs in systemic infection with A. fumigatus. The clinical significance of results obtained in these two studies is unknown.

Concomitant use of the following agents with fluconazole is contraindicated:

Astemizole
Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsade de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see CONTRAINDICATIONS).

Cisapride.
Fluconazole 200 mg daily increased the AUC and Cmax of cisapride (20mg four times daily) both after a single dose (AUC increased 101% and Cmax increased 91%) and multiple doses (AUC increased 192% and Cmax increased 154%). A significant prolongation in QTc interval was recorded. 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 arrythmias or had serious underlying illness. Coadministration of cisapride is contraindicated in patients receiving fluconazole (see Contraindications).

Terfenadine
Because of the occurrence of serious dysrhythmias secondary to prolongation of the QT_c interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study of a fluconazole 200mg daily dose failed to demonstrate a prolongation in QT_c interval. Another study of a fluconazole 400 and 800mg daily dose demonstrated that fluconazole taken in doses of 400mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400mg or greater of terfenadine is contraindicated. The coadministration of fluconazole at doses lower

then 400mg per day with terfinadine should be carefully monitored (see CONTRAINDICATIONS).

Pimozide
Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT_c prolongation and rare occurrences of *torsade de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see CONTRAINDICATIONS).
Quinidine
Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated.

Concomitant use of the following other medicinal products cannot be recommended:

Erythromycin
Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsade de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated.

Interaction of fluconazole with the following agents may result in increased exposure to these drugs. Careful monitoring and/or dosage adjustment should be considered:

Calcium channel blockers
Certain dihydropyridine calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Carbamazepine
Azole antifungals may raise carbamazepine plasma concentrations. Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. Since high plasma concentrations of carbamazepine and/or carbamazepine-10, 11-epoxy may result in adverse effects (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or plasma concentrations monitored when used concomitantly with fluconazole.

Celecoxib
During concomitant treatment with fluconazole (200mg daily) and celecoxib (200mg) the celecoxib C_{max} and AUC increased by 68% and 134% respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

Cyclosporin.
Fluconazole significantly increases the concentration and AUC of cyclosporin. This combination may be used by reducing the dosage of cyclosporine depending on cyclosporine concentration.

Cyclophosphamide
Combination therapy with cyclophosphamide and fluconazole results in increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Everolimus
Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Fentanyl
One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Futhermore, in a randomized crossover study with twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

Halofantrine
Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided.

HMG-CoA reductase inhibitors
The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolized through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored.

Losartan
Fluconazole inhibits the metabolism of losartan to its active metabolite (E-3174) which is responsible for most of the angiotensin II-receptor antagonism that occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone
Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs
The C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82% respectively, when fluconazole was

coadministered with racemic ibuprofen (400mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornexicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed

Oral hypoglycaemic agents. The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycaemic agents tolbutamide, glipizide and glibenclamide were examined in three placebo- controlled crossover studies in normal volunteers. All subjects received the sulfonylurea alone and following treatment with fluconazole 100mg as a single daily oral dose for seven days. Fluconazole administration resulted in significant increases in Cmax and AUC of the sulfonylurea. 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 sulfonylureas (eg. Glimepiride and gliclazide) and the thiazolidinediones (eg piogiltazone and rosiglitazone), which are metabolised by these enzymes. When fluconazole and sulfonylureas or thiazolidinediones are coadministered, blood glucose concentrations should be monitored carefully. The possibility of a hypoglycaemic episode should be borne in mind.

Phenytoin.
Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone
There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin
There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80%. 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.

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 150mg resulted in modest increases in midazolam concentrations and psychomotor effects following oral administration of 10mg 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 7.5mg, but only modest increases that are not likely to be clinically significant following intravenous infusion of midazolam 0.05mg/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. Fluconazole increases the AUC of triazolam (single dose) by approximately 50% C_{max} with 20-32% and increases the half life by 25-50% due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

Saquinavir
Fluconazole increases the AUC of saquinavir by approximately 50%, increases C_{max} by approximately 55% and decreases clearance of saquinavuir by approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

Sirolimus
Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

Sulfonylureas
Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g. chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during coadministration.

Tacrolimus.
Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

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 of theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole and therapy modified appropriately if signs of toxicity develop.

Tofacitinib
Exposure of tofacitinib is increased when tofacitinib is coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole). Dosage adjustment of tofacitinib may be necessary.

Vinca Alkaloids
Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect of CYP3A4.

Vitamin A
Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole
(CYP2C9, CYP2C19 and CYP3A4 inhibitor): Concomitant administration of voriconazole and fluconazole at any dose is not recommended.

Warfarin.
A single dose of warfarin 15mg given to normal volunteers, following 14 days of orally administered fluconazole 200mg resulted in a 12% increase in the prothrombin time response (area under the prothrombin time-time curve). One in 13 subjects experienced a twofold increase in prothrombin time response. In postmarketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melaena) 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.
Fluconazole increases C_{max} and AUC by 85% and 75% of zidovudine, respectively due to decrease in oral zidovudine clearance of approximately 45%. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse effects. Dosage reduction of zidovudine may be considered.

Minor or no significant pharmacokinetic interactions that require no dosage adjustment.

Oral contraceptives. Oral contraceptives were administered as a single dose both before and after oral administration of fluconazole 50mg once daily for ten days in ten healthy women. There was no significant difference in ethinyloestradiol or levonorgestrel AUC after the administration of fluconazole 50mg. The mean increase in ethinyloestradiol AUC was 6% (range:-47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

In a second study, 25 normal females received daily doses of fluconazole 200mg or placebo for two ten day periods. The treatment cycles were one month apart with all subjects receiving fluconazole during one cycle and placebo during the other. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyloestradiol were administered on the final treatment day (day 10) of both cycles. Following administration of fluconazole 200mg, the mean percentage increase in AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyloestradiol compared to placebo was 38% (range: -11 to 101%). Both of these increases were statistically significantly different from placebo.
In a third study 21 healthy women received weekly doses of fluconazole 300 mg and single doses of ethinyloestradiol 35 microgram and norethindrone 0.5 mg. AUC of ethinyloestradiol was increased by 24% (range: 3 to 59%) and AUC of norethindrone was increased by 13% (range: -5 to 36%).
Multiple doses of fluconazole may increase exposure to hormone levels in women taking oral contraceptives and are unlikely to result in decreased efficacy of the oral contraceptive.

Two way interactions.
Minor or no significant pharmacokinetic interactions that require no dosage adjustment.

Azithromycin.
An open label, randomised, three way cross study in 18 healthy subjects assessed the effect of a single oral dose of azithromycin 1,200mg on the pharmacokinetics of a single oral dose of fluconazole 800mg as well as the effects of fluconazole on the pharmacokinetics of azithromycin. The estimated ratio of the mean AUC of fluconazole coadministered with azithromycin to fluconazole administered alone was 101%. The estimated ratio of the mean AUC of azithromycin coadministered with fluconazole to azithromycin administered alone was 107%. The estimated ratio of the mean Cmax of fluconazole coadministered with azithromycin to fluconazole administered alone was 104%. The estimated ratio of the mean C_{max} of azithromycin coadministered with fluconazole to azithromycin administered alone was 82%.

Table 2. Guidance on the clinical management of drug interactions.

Contraindications	**Dose adjustment of fluconazole**	**Dose adjustment and/or monitoring of other drugs**	**No dose adjustment of fluconazole or other drugs**
Cisapride	Hydrochlorothiazide[1] Rifampicin[2]	Benzodiazepines (short-acting)[5] Carbamazepine[4] Cyclosporin[4] Oral hypoglycaemics[3] Phenytoin[4] Rifabutin[5] Tacrolimus[5] Theophylline[5] Warfarin[6] Zidovudine[5]	Antacids Azithromycin Cimetidine Oral contraceptives

1. Fluconazole blood levels increased
2. Fluconazole blood levels decreased
3. Carefully monitor blood glucose levels

4. Carefully monitor plasma drug levels
5. Carefully monitor patients for signs of toxicity or adverse events
6. Carefully monitor patient's prothrombin time

ADVERSE EFFECTS

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

MedDRA System Organ Class *Frequency**	**Adverse Drug Reactions**
Eye disorders *Uncommon*	Abnormal vision
Gastrointestinal disorders *Common* *Uncommon*	Nausea, abdominal pain, diarrhoea, dyspepsia Constipation, flatulence, vomiting, loose stools, dry mouth
General disorders and administration site conditions *Uncommon*	Thirst, fatigue, malaise, pain, rigors, asthenia, fever
Infections and infestations *Uncommon*	Pharyngitis, herpes simplex
Metabolism and nutritional disorders *Uncommon*	Anorexia
Musculoskeletal and connective tissue disorders *Uncommon*	Back pain, myalgia
Nervous system disorders *Common* *Uncommon*	Headache Dizziness, vertigo, hyperkinesia, hypertonia, taste perversion, visual field defect
Psychiatric disorders *Uncommon*	Insomnia, nervousness, somnolence
Renal and urinary disorders *Uncommon*	Polyuria, renal pain
Reproductive system and breast disorders *Uncommon*	Intermenstrual bleeding, dysmenorrhoea, leukorrhoea, menorrhagia, uterine spasm, vaginal disorders, female sexual dysfunction

Skin and subcutaneous tissue disorders *Uncommon*	Pruritis, genital pruritis, rash, erythematous rash, dry skin, abnormal skin odour, urticaria
Vascular disorders *Uncommon*	Flushing, hot flushes
Hepato-biliary disorders *Common* *Uncommon* *Rare*	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased Cholestasis, jaundice, bilirubin increased Hepatic toxicity, including rare cases of fatalities. Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage
Cardiac disorders *Rare*	Torsade de pointes, QT prolongation

*Frequencies are categorised as follows: very common ≥ 10%; common from ≥ 1% to < 10%; uncommon ≥ 0.1% to < 1%; rare from 0.01% to < 0.1%.

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

Blood and lymphatic system. Leucopenia including neutropenia and agranulocytosis, thrombocytopenia.
Cardiovascular. Ventricular arrhythmia (QT prolongation, torsades de pointes (see Precautions).
Nervous system. Seizures.
Immune system. 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. Fixed drug eruption, urticaria, acute generalised exanthematous pustulosis. Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

Flufeme is administered orally.

Adults. For vaginal candidiasis, fluconazole 150mg should be administered as a single oral dose.

In those patients who responded to treatment, the median time to onset of symptom relief was one day (range: 0.04 – 9 days) and to complete symptom relief was two days (range: 0.5 – 20 days).

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

Impaired renal function. Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single dose therapy are necessary.

OVERDOSAGE

The minimal lethal human dose has not been established. There have been reports of overdosage with fluconazole, and in one case a 42 year old patient infected with HIV developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8,200mg of fluconazole. The patient was admitted to hospital, and his condition resolved within 48 hours. Signs and symptoms are likely to be an extension of those under ADVERSE EFFECTS.

In mice and rats receiving very high doses of fluconazole, clinical effects in both species included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex and cyanosis; death was sometimes preceded by clonic convulsions.

Treatment

There is no specific antidote. Treatment is symptomatic and supportive, including respiratory and cardiovascular function. Monitor for hypokalaemia and elevated liver enzymes; and obtain a full blood count to monitor for possible thrombocytopenia and agranulocytosis.

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 on 13 11 26 for advice on management of an overdose.

PRESENTATION

Flufeme 150mg capsules: Hard gelatin capsules, white cap white body with the imprint FC150. Available is a blister pack of 1 capsule.

STORAGE CONDITIONS

Store below 25°C.

SPONSOR

Sandoz Pty. Ltd.
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
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Tel: 1800 634 500

Poison Schedule

Flufeme 150mg capsule (Pack size of 1 capsule), AUST R: 132827

Schedule 3 – Pharmacist Only Medicine

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