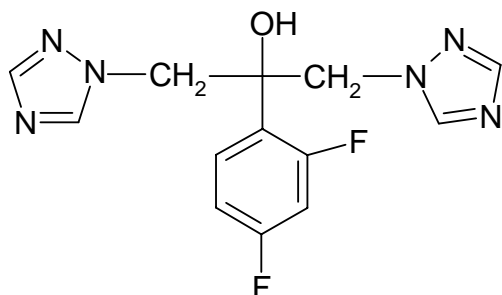


PRODUCT INFORMATION FLUCONAZOLE WINTHROP 100mg and 200mg CAPSULES

NAME OF THE MEDICINE

Fluconazole

2-(2,4-difluorophenyl)-1,3-bis (1H-1,2,4-triazol-1-yl) -2-propanol.



CAS: 86386-73-4

Empirical formula: C₁₃H₁₂F₂N₆O

MW: 306.3

DESCRIPTION

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

Fluconazole Winthrop capsules also contain inactive ingredients:

Lactose, starch-maize, magnesium stearate, colloidal anhydrous silica, sodium lauryl sulfate, titanium dioxide, gelatin, Indigo Carmine (100mg and 200mg capsules only) and Brilliant Scarlet 4R (200mg capsules only). Printing Ink: Shellac, black iron oxide, propylene glycol.

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 400mg 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 is markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of Fluconazole Winthrop may need to be reduced in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). 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, once daily and once weekly dosing for all other indications.

Children

There are differences in the pharmacokinetics of fluconazole between adults and children, with children (after the neonatal period) generally having a faster elimination rate and larger volume of distribution than in adults. These differences result in less accumulation on multiple dosing in children, with steady-state achieved faster than in adults. Neonates have reduced elimination rates relative to adults and even higher volumes of distribution in comparison with older children. During the first two weeks after birth, the clearance of fluconazole increases (and the half-life is decreased) as renal function develops. The half-life obtained in infants was consistent with that found in older children, although the volume of distribution was higher. During the first year of life, the pharmacokinetics of fluconazole is similar to older children. No marked sex related differences in pharmacokinetics are evident in children.

In children the following mean pharmacokinetic data have been reported (see Table 1).

Table 1: Fluconazole – Mean pharmacokinetic data for children

Age	Dose (mg/kg)	Clearance (mL/min/Kg)	Half-life (Hours)	C _{max} (µg/m)	Vd _{ss} (L/kg)
9 months-13 years	Single oral				
	2mg/kg	0.40	25.0	2.9	-
	8mg/kg	0.51	19.5	9.8	-
5 years-15 years	Multiple I.V				
	2mg/kg	0.49	17.4	5.5	0.722
	4mg/kg	0.59	15.2	11.4	0.729
	8mg/kg	0.66	17.6	14.1	1.069

Clearance corrected for bodyweight was not affected by age in these studies. Mean body clearance in adults is reported to be 0.23mL/minute/kg.

In premature newborn infants (gestational age of 26 to 29 weeks), the mean clearance within 36 hours of birth was 0.180mL/minute/kg, which increased with time to a mean of 0.218mL/minute/kg six days later and 0.333mL/minute/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later.

INDICATIONS

Orally for treatment of cryptococcal meningitis in patients who are unable to tolerate amphotericin B. *Note.* Data suggest that the clinical efficacy of fluconazole is lower than that of amphotericin B in the treatment of the acute phase of cryptococcal meningitis.

Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with acquired immune deficiency syndrome (AIDS).

Treatment of oropharyngeal and oesophageal candidiasis in AIDS and other immunosuppressed patients.

Secondary prophylaxis of oropharyngeal candidiasis in patients with human immunodeficiency virus (HIV) infection.

Serious and life threatening *Candida* infections in patients who are unable to tolerate amphotericin B. *Note.* It remains to be shown that fluconazole is as effective as amphotericin B in the treatment of serious and life threatening *Candida* infections. Until such data are available, amphotericin B remains the drug of choice.

Vaginal candidiasis, when topical therapy has failed.

Treatment of extensive tinea corporis, extensive tinea cruris and extensive tinea pedis infections in immunocompetent patients in whom topical therapy is not a practical treatment option. Usually, topical therapy should be attempted first because oral therapy has a less favourable ratio of benefits to risks. (See ADVERSE EFFECTS.)

CONTRAINDICATIONS

Known sensitivity to fluconazole, related azole compounds or any of the excipients of Fluconazole Winthrop.

Coadministration of terfenadine is contraindicated in patients receiving fluconazole continuously at doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Co-administration of other drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as cisapride, astemizole, 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 hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed.

Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe liver injury. Fluconazole should be discontinued 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. If a rash that is attributable to fluconazole develops in a patient treated for a superficial fungal infection, fluconazole 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 (see ADVERSE EFFECTS).

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 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 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9 and CYP3A4 should be monitored (See Interactions with other medicines).

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

Elderly patients with renal impairment

Dosage should be adjusted for elderly patients with renal impairment (see DOSAGE AND ADMINISTRATION).

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)

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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 800mg/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.

Use in pregnancy should be avoided except in patients with severe or potentially life threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the foetus.

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

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 C_{max} 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 a moderate inhibitor of CYP3A4. In addition to the observed/documentated interactions mentioned below, there is a risk of increased plasma concentration of other

compounds metabolized by CYP2C9 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.

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 additive 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 C_{max} of cisapride (20mg four times daily) both after a single dose (AUC increased 101% and C_{max} increased 91%) and multiple doses (AUC increased 192% and C_{max} increased 154%). A significant prolongation in QT_c 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 arrhythmias 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 than 400mg per day with terfenadine 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. Increase 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).

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. This combination should be avoided.

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 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

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 cyclosporin depending on cyclosporin 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.

Fentanyl

One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, 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.

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 creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

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, lornoxicam, 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 C_{max} 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. When fluconazole and sulfonylureas are coadministered, blood glucose concentrations should be monitored carefully and the dose of the sulfonylurea adjusted accordingly.

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. 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. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. There have been reports of sleepiness and disturbed consciousness in patients taking fluconazole for systemic mycoses and triazolam. However, in most of these cases the patients had serious underlying illnesses and/or concomitant therapies that could have contributed to the reported events, and a relationship with a fluconazole-triazolam interaction has not been established. 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 saquinavir 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.

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.

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 two-fold 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 openlabel, randomised, threeway 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 C_{max} 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

The safety profile of fluconazole appears similar in adults and children. The profile established for adults, given different dosage regimens and for different indications is given below.

Multiple daily dosing for treatment of oral and oropharyngeal candidiasis, cryptococcal meningitis or systemic candidiasis

Fluconazole is generally well tolerated. 16% of over 4,000 patients treated in clinical trials of seven days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% due to laboratory abnormalities.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

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. In combined clinical trials and marketing experience, the spectrum of hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Elevations in plasma levels of hepatic enzymes have been observed both in otherwise healthy patients and in patients with underlying disease (see PRECAUTIONS). There have been rare cases of serious hepatic reactions during treatment with fluconazole (see PRECAUTIONS). Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. In addition, transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of fluconazole.

In two comparative trials evaluating the efficacy of fluconazole for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than eight times the upper limit of normal was approximately 1% in fluconazole treated patients in the premarketing clinical trials which included patients with severe underlying disease (predominantly AIDS or malignancies), most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampicin, phenytoin, isoniazid, valproic acid or oral sulfonylurea hypoglycaemic agents.

Other adverse effects observed include the following:

MedDRA System Organ Class <i>Frequency*</i>	Adverse Drug Reactions
Blood and lymphatic system disorders <i>Rare</i>	Leukopenia (including neutropenia and agranulocytosis), thrombocytopenia
Gastrointestinal disorders <i>Common</i>	Nausea, vomiting, abdominal pain, diarrhoea
Immunological system disorders <i>Rare</i>	

Metabolism and nutritional disorders <i>Common</i>	Headache
<i>Uncommon</i>	Seizures, dizziness, paraesthesia, taste perversion
<i>Rare</i>	Tremor
Skin and subcutaneous tissue disorders <i>Common</i>	Rash
<i>Rare</i>	Angiodema, exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necrolysis (see PRECAUTIONS), alopecia

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

Single 150 mg dose for vaginal candidiasis

MedDRA System Organ Class <i>Frequency*</i>	Adverse Drug Reactions
Eye disorders <i>Uncommon</i>	Abnormal vision
Gastrointestinal disorders <i>Common</i>	Nausea, abdominal pain, diarrhoea, dyspepsia
<i>Uncommon</i>	Constipation, flatulence, vomiting, loose stools, dry mouth
General disorders and administration site conditions <i>Uncommon</i>	Thirst, fatigue, malaise, pain, rigors, asthenia, fever
Infections and infestations <i>Uncommon</i>	Pharyngitis, herpes simplex
Metabolism and nutritional disorders <i>Uncommon</i>	Anorexia
Musculoskeletal and connective tissue disorders <i>Uncommon</i>	Back pain, myalgia
Nervous system disorders <i>Common</i>	Headache
<i>Uncommon</i>	Dizziness, vertigo, hyperkinesia, hypertonia, taste perversion, visual field defect
Psychiatric disorders <i>Uncommon</i>	Insomnia, nervousness

Renal and urinary disorders <i>Uncommon</i>	Polyuria, renal pain
Reproductive system and breast disorders <i>Uncommon</i>	Intermenstrual bleeding, dysmenorrhea, leukorrhoea, menorrhagia, uterine spasm, vaginal disorders, female sexual dysfunction
Skin and subcutaneous tissue disorders <i>Uncommon</i>	Pruritis, genital pruritis, rash, erythematous rash, dry skin, abnormal skin odour, urticaria
Vascular disorders <i>Uncommon</i>	Flushing, hot flushes
Hepato-biliary disorders <i>Common</i> <i>Uncommon</i> <i>Rare</i>	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 <i>Rare</i>	Torsade de pointes, QT prolongation

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

Dermal therapeutic studies in patients treated with 150 mg weekly

MedDRA System Organ Class <i>Frequency*</i>	Adverse Drug Reactions
Gastrointestinal disorders <i>Common</i>	Abdominal pain, dyspepsia
Investigations <i>Uncommon</i>	Elevation of transaminase $>2-3$ x upper limit of normal
Nervous system disorders <i>Common</i> <i>Uncommon</i>	Headache Paraesthesia, somnolence
Psychiatric disorders <i>Uncommon</i>	Insomnia, somnolence
Skin and subcutaneous tissue disorders <i>Uncommon</i>	Pruritis, urticaria, increased sweating, drug eruption

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

Children

In clinical studies, 562 children, from birth to 17 years, received doses from 1 to 12mg/kg/day, for up to 129 days. The majority of patients (n = 522) received 2 to 8mg/kg/day for up to 97 days. Overall, approximately 10.3% experienced adverse events which were considered treatment related. The incidence of these adverse reactions and laboratory abnormalities do not suggest any marked difference between the paediatric population relative to the adult population. Based on this clinical trial data, the following adverse events were considered treatment related.

MedDRA System Organ Class <i>Frequency*</i>	Adverse Drug Reactions
Cardiac disorders <i>Uncommon</i>	Cardiomyopathy
Ear and labyrinth disorders <i>Uncommon</i>	Deafness
Gastrointestinal disorders <i>Common</i> <i>Uncommon</i>	Vomiting, diarrhoea, abdominal pain Nausea, dyspepsia, ileus, stomatitis, loose stools
Hepatobiliary disorders <i>Uncommon</i>	Hepatocellular damage, jaundice
Metabolism and nutrition disorders <i>Uncommon</i>	Anorexia
Nervous system disorders <i>Uncommon</i>	Headache, taste perversion
Respiratory, thoracic and mediastinal disorders <i>Uncommon</i>	Hypoxia, respiratory disorder
Skin and subcutaneous tissue disorders <i>Uncommon</i>	Rash (erythematous & maculo-papular), pruritis, purpura
Vascular disorders <i>Uncommon</i>	Hypertension

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

Postmarketing experience

In addition, the following adverse events have occurred during postmarketing.

Cardiovascular. Ventricular arrhythmia (QT prolongation, torsades de pointes) (see PRECAUTIONS).

Central nervous system. Dizziness.

Gastrointestinal. Dyspepsia, vomiting.

Immunological. Anaphylaxis (including face oedema, angioedema and pruritus).

Metabolic. Hypercholesterolaemia, hypertriglyceridaemia and hypokalaemia.

Hepatobiliary. Hepatocellular necrosis.

Dermatological. Fixed drug eruption, urticaria, acute generalized exanthematous pustulosis.

DOSAGE AND ADMINISTRATION

Fluconazole Winthrop is normally administered orally. If oral administration is not possible, it may be administered by intravenous infusion. Since oral absorption is rapid and almost complete, there is no need to change the daily dosage on transferring from the intravenous to the oral route or vice versa.

The daily dose of Fluconazole Winthrop should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis often require maintenance therapy to prevent relapse.

Adults

Cryptococcal meningitis in patients who are unable to take or tolerate amphotericin B

The usual dose is 400mg on the first day followed by 200mg once daily. A dosage of 400mg once daily may be used, based on medical judgment of the patient's response to therapy. Patients not responding to treatment for up to 60 days would appear unlikely to respond to Fluconazole Winthrop.

Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but should continue for ten to twelve weeks after cerebrospinal fluid becomes culture negative. Negative serology does not necessarily indicate eradication of the disease; a proportion of such patients relapse in due course.

Prevention of relapse of cryptococcal meningitis in patients with AIDS

After the patient receives a full course of primary therapy, Fluconazole Winthrop may be administered at a daily dose of 100 to 200mg.

Treatment of oropharyngeal and oesophageal candidiasis

The recommended dose for oropharyngeal candidiasis is 100mg on the first day followed by 50mg once daily. For the treatment of oesophageal candidiasis the recommended dose is 200mg on the first day followed by 100 mg once daily. Clinical evidence of candidiasis usually resolves within several days, but treatment should be continued for at least two to three weeks, especially in patients with severely compromised immune function. Patients with severe oesophageal candidiasis may need treatment to be continued for two weeks following resolution of symptoms. Approximately half of the clinically cured patients remain colonised.

Secondary prophylaxis against oropharyngeal candidiasis in patients with HIV infection

The recommended dose is 150mg as a single dose once weekly.

Serious and life threatening candidal infections in patients unable to tolerate amphotericin B

The usual dose is 400mg on the first day followed by 200mg daily. Depending on the clinical response, the dose may be increased to 400mg daily. Duration of treatment is based on clinical response; patients should be treated for a minimum of four weeks and for at least two weeks following resolution of symptoms.

Vaginal candidiasis when topical therapy has failed

Fluconazole Winthrop 150 mg 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).

Extensive tinea infections, severe tinea pedis

For extensive tinea infections (tinea corporis, tinea cruris), or severe tinea pedis in immunocompetent patients in whom topical therapy is not practical, the recommended dosage is 150 mg once weekly for four weeks.

Children

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole Winthrop is administered as a single dose each day.

Treatment of mucosal candidiasis

The recommended dosage is 3 mg/kg daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady-state levels more rapidly.

Treatment of systemic candidiasis and cryptococcal infection

The recommended dosage is 6 to 12 mg/kg daily, depending on the severity of the disease.

For children with impaired renal function the daily dose should be reduced in accordance with the guidelines given for adults.

Children 4 weeks of age and younger

Neonates excrete fluconazole slowly. In the first two weeks of life the same mg/kg dosing as in older children should be used but administered every 72 hours. During weeks 3 and 4 of life the same dose should be given every 48 hours.

Elderly

Dosage should be adjusted for elderly patients with renal impairment (see Renal impairment, below).

Impaired renal function

Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single dose therapy are necessary. In multiple dose treatment of patients with renal impairment, normal doses should be given on days 1 and 2 of treatment and thereafter the dosage intervals or the daily dose should be modified in accordance with creatinine clearances as in Table 3.

Table 3: Fluconazole Winthrop dosage according to creatinine clearance.

Creatinine clearance (mL/minute)	Dosage intervals/daily dose
>50	24 hours (normal dosage regimen)
21-50	48 hours or half normal daily dose
11-20	96 hours or one quarter normal daily dose

For patients receiving regular dialysis, administer one recommended dose after every dialysis session.

These are suggested dose adjustments based on pharmacokinetics following administration of single doses. Further adjustment may be needed depending on clinical condition.

When serum creatinine is the only measure of renal function available, the Cockcroft-Gault equation should be used to estimate the creatinine clearance in mL/minute.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

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 8,200 mg 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.

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%.

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.

PRESENTATION AND STORAGE CONDITIONS

Fluconazole Winthrop 100mg capsules: Hard gelatin capsules, blue cap white body with the imprint FC100. Available in blister packs of 28 capsules.

Fluconazole Winthrop 200mg capsules: Hard gelatin capsules, purple cap white body with the imprint FC200. Available in blister packs of 28 capsules.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Fluconazole Winthrop is supplied in Australia by:
sanofi-aventis australia pty ltd
12-24 Talavera Road, Macquarie Park, NSW 2113
Freecall No: 1800 818 806

Fluconazole Winthrop is supplied in New Zealand by:
sanofi-aventis new zealand limited
Auckland, New Zealand
Freecall No: 0800 283 684

POISON SCHEDULE OF THE MEDICINE

Fluconazole Winthrop 100mg and 200mg capsules (Pack size of 28 capsules):

Schedule 4 – Prescription Only Medicine

Date of TGA approval: 16/03/2007

Date of most recent amendment: 30/06/2010