

CANESORAL

Fluconazole

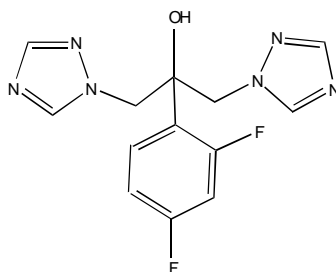
PRODUCT INFORMATION

Name of the Medicine

Active ingredient: Fluconazole

Chemical name: 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol

Structural formula:



Molecular formula: $C_{13}H_{12}F_2N_6O$

Molecular weight: 306.3

CAS Registry No.: 86386-73-4

Description

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

Each CANESORAL capsule contains fluconazole 150 mg as the active ingredient.

Other ingredients: gelatin, lactose, starch – maize starch, silicon dioxide, magnesium stearate, sodium lauryl sulfate, titanium dioxide, TekPrint SW-9008 black printing ink, TekPrint SW-9009 black printing ink.

Pharmacology

Pharmacodynamics

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 50 mg daily given 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 50 mg do not affect its metabolism.

Pharmacokinetics and Metabolism

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 1 and 2 hours post 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 5-10 days with oral doses of 50-400 mg once daily. Steady-state levels are approximately 2.5 times the levels achieved with single doses. 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 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. The dose of fluconazole may need to be reduced in patients with impaired renal function (see **Dosage and Administration**). A 3-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.

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 adults.

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* spp., 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 above mentioned 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.

Indications

CANESORAL, given orally, is indicated for vaginal candidiasis.

Contraindications

CANESORAL is contraindicated in patients with known sensitivity to fluconazole, to related azole compounds or to any of its excipients.

Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study.

Coadministration of other drugs known to prolong the QT interval and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, pimozone and quinidine is contraindicated in patients receiving fluconazole (see **Precautions – Interactions with Other Medicines**).

Precautions

Anaphylaxis

Anaphylaxis has been reported in rare instances.

Hepatic Impairment

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 hepatic injury. CANESORAL should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see **Adverse Effects**).

Renal Impairment

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

Elderly Patients with Renal Impairment

Dosage should be adjusted for elderly patients with renal impairment (see **Dosage and Administration**).

Skin and Subcutaneous Tissue Disorders

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 serious cutaneous reactions to many drugs. If rash which is attributable to fluconazole develops in a patient treated for a superficial fungal infection, CANESORAL should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and CANESORAL discontinued if bullous lesions or erythema multiforme develop (see **Adverse Effects**).

QT Interval Prolongation

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. 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**).

CYP2C9 and CYP3A4 Interactions

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 **Precautions – Interactions with Other Medicines**).

Effect on Fertility

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 – Pharmacodynamics**).

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. 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.

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

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.

Carcinogenicity and Mutagenicity

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 2-7x 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.

Interactions with Other Medicines

Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP 2C and to a lesser extent the CYP 3A isoforms. Co-administration of fluconazole with some other drugs metabolised primarily by these P450 isoforms may result in altered plasma concentrations of these drugs that could change therapeutic effects and/or adverse event profiles.

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 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 CANESORAL.

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 100 mg and hydrochlorothiazide 50 mg for 10 days in normal volunteers resulted in an increase of 41% in C_{max} and an increase of 43% in AUC of fluconazole, compared to fluconazole given alone. Overall the plasma concentrations of fluconazole were approximately 3.26 to 6.52 $\mu\text{mol/L}$ 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 200 mg 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 (100 mg) with cimetidine (400 mg) resulted in a 13% reduction in AUC and a 21% reduction in C_{max} of fluconazole. Administration of an antacid containing aluminium and magnesium hydroxides immediately prior to a single dose of fluconazole (100 mg) 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 metabolised 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 studies is unknown.

Concomitant use of the following agents with fluconazole is contraindicated:

Cisapride: Fluconazole 200 mg daily increased the AUC and C_{max} of cisapride (20 mg 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 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 arrhythmias or had serious underlying illness. The co-administration of fluconazole and cisapride is contraindicated (see

Contraindications).

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

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**).

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 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:

Benzodiazepines (short acting): 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 150 mg resulted in modest increases in midazolam concentrations and psychomotor effects following oral administration of 10 mg that may not be clinically significant. At doses used to treat systemic mycoses, fluconazole resulted in substantial increase in midazolam concentrations and psychomotor effects following oral administration of 7.5 mg, but only modest increases that are not likely to be clinically significant following intravenous infusion of midazolam 0.05 mg/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 true 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 monitoring the patient's response. 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.

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.

Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg) 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 an 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 metabolised 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.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) 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 (NSAIDs): 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 100 mg as a single daily oral dose for 7 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. As fluconazole is a potent inhibitor CYP 2C8 and CYP 2C9, it may also interact with other sulfonylureas (eg. glimepiride and gliclazide) and the thiazolidinediones (eg. pioglitazone and rosiglitazone), which are metabolised by these enzymes. When fluconazole and sulfonylureas or thiazolidinediones are coadministered, blood glucose concentrations should be monitored carefully and the dose of the sulphonylurea 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 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.

Saquinavir: Fluconazole increases the AUC of saquinavir and decreases clearance of saquinavir 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 200 mg 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 on 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 15 mg given to normal volunteers, following 14 days of orally administered fluconazole 200 mg 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 post-marketing 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 of zidovudine, respectively, due to decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.

Carbamazepine: Azole antifungals may raise carbamazepine plasma concentrations. 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.

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 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinylestradiol or levonorgestrel AUC after the administration of 50 mg of fluconazole. The mean increase in ethinylestradiol AUC was 6% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

In a second study, twenty-five normal females received daily doses of 200 mg fluconazole 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 ethinylloestradiol were administered on the final treatment day (day 10) of both cycles. Following administration of 200 mg of fluconazole, the mean percentage increase in AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinylloestradiol 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 300 mg weekly doses of fluconazole and single doses of ethinylloestradiol 35 microgram and norethindrone 0.5 mg. AUC of ethinylloestradiol 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 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole 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%.

Guidance on the Clinical Management of Drug Interactions

Contraindications	Dose adjustments 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 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

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.

Adverse Effects

Fluconazole is generally well tolerated.

Common adverse events (>1% and <10%) observed during vaginal candidiasis clinical trials and associated with fluconazole.

Nervous System Disorders: Headache

Gastrointestinal Disorders: Nausea, abdominal pain, diarrhoea, dyspepsia

Hepatobiliary Disorders: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased

Uncommon adverse events (>0.1% and <1%) observed during vaginal candidiasis clinical trials associated with fluconazole.

Eye Disorders: Abnormal vision

Skin and Subcutaneous Tissue Disorders: Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria

Nervous System Disorders: Dizziness, vertigo, hyperkinesia, hypertonia, taste perversion, visual field defect

Gastrointestinal: Constipation, dry mouth, flatulence, vomiting, loose stools

Infections and Infestations: Pharyngitis, herpes simplex

Metabolism and Nutrition Disorders: Anorexia

Psychiatric Disorders: Insomnia, nervousness

Reproductive System and Breast Disorders: Intermenstrual bleeding, dysmenorrhoea, leucorrhoea, menorrhagia, uterine spasm, vaginal disorder, female sexual dysfunction

Vascular Disorders: Flushing, hot flushes

Hepatobiliary Disorders: Cholestasis, jaundice, bilirubin increased

Renal and Urinary Disorders: Polyuria, renal pain

General Disorders and Administration Site Conditions: Fatigue, hot flushes, malaise, back pain, herpes simplex, pain, rigors, thirst, asthenia, fever

Musculoskeletal and Connective Tissue Disorders: Back pain, myalgia

Rare adverse events (>0.01% and <0.1%) observed during vaginal candidiasis clinical trials associated with fluconazole.

Hepatobiliary Disorders: Hepatic toxicity, including rare cases of fatalities. Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage

Cardiac Disorders: Torsade de pointes, QT prolongation

Post-Marketing Experience

Cardiac Disorders: Torsade de pointes (see **Precautions**)

Gastrointestinal Disorders: Dyspepsia, vomiting

Hepatobiliary Disorders: Hepatocellular necrosis

Immune System Disorders: Anaphylaxis (including face oedema, angioedema and pruritus)

Investigations: QT prolongation (see **Precautions**)

Metabolism and Nutrition Disorders: Hypercholesterolaemia, hypertriglyceridaemia and hypokalaemia

Nervous System Disorders: Dizziness

Dosage and Administration

CANESORAL is administered orally.

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

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

Renal Impairment. Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single-dose therapy are necessary in patients with minor to moderate renal impairment.

Overdosage

The minimal lethal human dose has been not 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**.

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 131 126 for advice on the management of an overdose.

Presentation and Storage Conditions

CANESORAL A size 1, white opaque body and white opaque cap, hard gelatin capsule, printed with “FC 150” and “G” on both body and cap in black ink.

CANESORAL is available in blister packs of 1 capsule.

Store below 25°C.

Name and Address of the Sponsor

Bayer Australia Limited
ABN 22 000 318 714

Consumer Care Business Group
875 Pacific Highway
Pymble NSW 2073

Poison Schedule of the Medicine

Schedule 3 (Pharmacist Only Medicine).

Date of Approval

Approved by the Therapeutic Goods Administration on: 22 February 2011