AUSTRALIAN PRODUCT INFORMATION

DIZOLE ONE®

(Fluconazole) capsule, hard

1 NAME OF THE MEDICINE

Fluconazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg of Fluconazole as the active ingredient.

Excipients with known effect: DIZOLE ONE also contains sulfites, phenylalanine and sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

DIZOLE ONE 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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DIZOLE ONE, given orally, is indicated for vaginal candidiasis.

4.2 DOSE AND METHOD OF ADMINISTRATION

DIZOLE ONE is administered orally.

Adults

For vaginal candidiasis when topical therapy has failed, fluconazole 150 mg (DIZOLE ONE) 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 doctor 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.

4.3 CONTRAINDICATIONS

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

Co-administration of other drugs known to prolong the QT interval and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine is contraindicated in patients receiving fluconazole (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Co-administration 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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. DIZOLE ONE should not be used again if a rash develops that is attributable to fluconazole.

Anaphylaxis

Anaphylaxis has been reported in rare instances.

QT Interval Prolongation

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4 (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). 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. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and torsades de pointes. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Terfenadine

The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

CYP2C9, CYP2C19 and CYP3A4 Interactions

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 **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Adrenal insufficiency

Adrenal insufficiency has been reported in patients receiving other azoles (e.g., ketoconazole). Reversible cases of adrenal insufficiency were reported in patients receiving fluconazole.

Lactose

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

Candidiasis

Studies have shown an increasing prevalence of infections with Candida species other than C. albicans. These are often resistant (e.g., C. krusei and C. auris) or show reduced susceptibility to fluconazole (C. glabrata). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribes are advised to take into account the prevalence of resistance in various Candida species to fluconazole (see **Section 5.1 PHARMACODYNAMIC PROPERTIES**).

Use in 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 hepatoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed.

DIZOLE ONE should not be used again if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see **Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**).

Use in Renal impairment

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

Use in the Elderly

No adjustments in single-dose therapy are necessary in elderly patients with minor to moderate renal impairment.

Paediatric Use

DIZOLE ONE is not recommended for use in children.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 DIZOLE ONE.

Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP 2C and to a lesser extent the CYP 3A isoforms. 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.

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzymes 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 coadministered 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 to 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see **Section 4.3 CONTRAINDICATIONS**).

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. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving diuretics, although the prescriber should bear it in mind.

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.

Alfentanil

A study observed a reduction in clearance and distribution volume as well as prolongation of $T_{½}$ 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 increase QT prolongation. Caution must be exercised if the concomitant use of fluconazole and amiodarone is necessary, notably with high dose fluconazole (800 mg).

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 (amphotericin)

Concurrent administration of fluconazole and amphotericin B (amphotericin) 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.

Anticoagulants

In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experience as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored. Dose adjustment of warfarin may be necessary.

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*. Co-administration of fluconazole and astemizole is contraindicated (see **Section 4.3 CONTRAINDICATIONS**).

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. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

Carbamazepine

Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effects.

Calcium Channel Blockers

Certain 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.

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.

Cisapride

Cardiac events including torsades de pointes have been reported in patients receiving fluconazole and cisapride concomitantly. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. The co-administration of cisapride is contraindicated in patients receiving fluconazole (see **Section 4.3 CONTRAINDICATIONS**).

Ciclosporin

A kinetic study in renal transplant patients found fluconazole 200 mg daily to slowly increase ciclosporin concentrations. However, in another multiple dose study with 100 mg daily, fluconazole did not affect ciclosporin levels in patients with bone marrow transplants. Ciclosporin plasma concentration monitoring in patients, with or without impaired renal function, receiving fluconazole is recommended.

Cyclophosphamide monohydrate

Combination therapy with cyclophosphamide monohydrate 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.

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. Co-administration of fluconazole and erythromycin is contraindicated (see **Section 4.3 CONTRAINDICATIONS**).

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. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/Rhabdomyolysis is diagnosed or suspected. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.

Ibrutinib

Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib as instructed in ibrutinib prescribing information and provide close clinical monitoring.

Ivacaftor (alone or combined with drugs in the same therapeutic class)

Coadministration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

Lemborexant

Concomitant administration of fluconazole increased lemborexant C_{max} and AUC by approximately 1.6- and 4.2-fold, respectively which is expected to increase risk of adverse reactions, such as somnolence. Avoid concomitant use of lemborexant.

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.

Lurasidone

Moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.

Methadone

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

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The Cmax and AUC of flurbiprofen were increased by 23% and 81%, respectively, when co-administered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] were increased by 15% and 82%, respectively, when fluconazole was co-administered with racemic ibuprofen (400 mg) 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 Contraceptives

Fluconazole at a dose of 50 mg for 10 days decreased the AUC for ethinylestradiol by 16%, but values for levonorgestrel were unchanged. There were no relevant effects on hormone level in the 50 mg fluconazole. At 200 mg daily, the AUCs of ethinylestradiol and levonorgestrel were increased 40% and 24%, respectively. Multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

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 of CYP2C8 and CYP2C9, it may also interact with other sulfonylureas (e.g. glimepiride and gliclazide) and the thiazolidinediones (e.g. pioglitazone and rosiglitazone), which are metabolised by these enzymes. When fluconazole and sulfonylureas or thiazolidinediones are co-

administered, blood glucose concentrations should be monitored carefully and the dose of the sulphonylurea adjusted accordingly. The possibility of a hypoglycemic episode should be borne in mind.

Phenytoin

Concomitant administration of oral fluconazole (200 mg) with phenytoin at steady state resulted in an average increase of 75% of phenytoin AUC values in normal volunteers. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended. Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

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. Co-administration of fluconazole and pimozide is contraindicated (see **Section 4.3 CONTRAINDICATIONS**).

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.

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. Co-administration of fluconazole and quinidine is contraindicated (see **Section 4.3 CONTRAINDICATION**).

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 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 midazolam 7.5 mg, but only modest increases that are not likely to be clinically significant following intravenous infusion of midazolam 0.05 mg/kg. 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.

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.

Rifampicin

Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the area under the concentration versus time curve (AUC) and a 20% shorter half-life of fluconazole in normal volunteers. In patients receiving concomitant rifampicin and depending on clinical circumstances, an increase of the fluconazole dose should be considered.

Saquinavir

Fluconazole increases the AUC of saquinavir with approximately 50%, Cmax with approximately 55% 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 co-administration.

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.

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 (see **Section 4.3 CONTRAINDICATIONS)**. The co-administration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

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.

Tofacitinib

Exposure is increased when tofacitinib is co-administered 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.

Tolvaptan

Exposure to tolvaptan is significantly increased (200% in AUC; 80% in Cmax) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse effects particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced and the patient managed cautiously.

Triazolam

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, Cmax with 20-32% and increases t½ by 25-50% due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam 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 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.

Voriconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Concurrent administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 6 healthy male subjects resulted in an increase in C, and AUC, of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended.

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.

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.

Physicians should be alert to the potential for drug-drug interactions, with other drugs for which pharmacokinetic drug-drug interaction studies have not been conducted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects 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 **Section 5.1 PHARMACODYNAMIC PROPERTIES**).

Use in Pregnancy

Pregnancy Category: 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 have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester.

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.

A study found any maternal exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion and that doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.

Fluconazole should not be used in women who are pregnant, or in women of childbearing potential unless adequate contraception is employed. Effective contraceptive measures should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Fluconazole is generally well tolerated.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**) have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

The following undesirable effects have been observed and reported during treatment with fluconazole with the following frequencies:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1,000 to <1/100)

Rare ≥1/10,000 to <1/1,000

Very rare <1/10,000

Not known cannot be estimated from the available data

System Organ Class	**Frequency**	**Undesirable Effects**
Blood and Lymphatic System Disorders	Rare	Leukopenia including neutropenia and agranulocytosis, thrombocytopenia
Immune System Disorders	Rare	Anaphylaxis (including face oedema, angioedema, urticaria and pruritus).
Metabolism and nutrition disorders	Uncommon	Thirst
	Rare	Hypercholesterolemia, hypertriglyceridemia and hypokalaemia.
Psychiatric Disorders	Uncommon	Insomnia, somnolence, nervousness, female sexual dysfunction
Nervous System Disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, flushing, hyperkinesia, hypertonia, taste perversion.
	Rare	Tremor
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiovascular Disorders	Rare	QT prolongation, torsade de pointes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Gastrointestinal Disorders	Common	Nausea, abdominal pain, diarrhoea, dyspepsia, vomiting
	Uncommon	Anorexia, dry mouth, flatulence, constipation, loose stools
Hepatobiliary disorders	Common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
	Uncommon	Cholestasis, jaundice, bilirubin increased
	Rare	Hepatic failure, hepatitis, hepatocellular necrosis, hepatocellular damage, hepatic toxicity, including rare cases of fatalities
Skin and subcutaneous tissue	Common	Rash

disorders	Uncommon	Pruritus, genital pruritus, erythematous rash, dry skin, abnormal skin odour, urticaria, increased sweating, drug eruption
	Rare	Alopecia, exfloiative skin disorders including Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, dermatitis exfoliative, face oedema
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and Connective Tissue Disorders	Uncommon	Myalgia
Urinary	Uncommon	Polyuria, renal pain
Reproductive	Uncommon	Intermenstrual bleeding, dysmenorrhoea, leucorrhoea, menorrhagia, uterine spasm, vaginal disorder
Respiratory	Uncommon	Pharyngitis
Special Senses	Uncommon	Abnormal vision, visual field defect
General Disorders and Administration Site Conditions	Uncommon	Fatigue, hot flushes, malaise, back pain, herpes simplex, pain, rigors, asthenia, fever

Paediatric Population

The pattern and incidence of adverse events and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

In the event of overdosage, symptomatic treatment (with supportive measures and gastric lavage if necessary) should be undertaken.

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%.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Clinical Trials

No data available.

Microbiology

Fluconazole administered orally or intravenously was active in a variety of animal models of fungal infections using standard laboratory strains of fungi.

In vitro, fluconazole displays antifungal activity against clinically common Candida species (including C. albicans, C. parapsilosis, C. tropicalis). C. glabrata shows reduced susceptibility to fluconazole while C. krusei and C. auris are resistant to fluconazole. The minimum inhibitory concentrations (MICs) and epidemiological cut-off value (ECOFF) of fluconazole for C. guilliermondii are higher than for C. albicans.

Fluconazole also exhibits *in vitro* activity against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

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 (amphotericin) 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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. Oral administration is not affected by concomitant food intake. 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%).

Distribution

Fluconazole has been found to achieve good penetration into all tissues and body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels.

Metabolism and Excretion

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, however, no adjustments in single-dose

therapy are necessary. 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 **Section 4.2 Dose and method of 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.

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Gelatin, lactose monohydrate, maize starch, silicon dioxide, magnesium stearate, sodium lauryl sulfate, titanium dioxide, TekPrint SW-9008 black printing ink, TekPrint SW-9009 black printing ink.

6.2 INCOMPATIBILITIES

See **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.**

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

DIZOLE ONE 150 mg is packaged in blister pack (PVC/Al or PVC/PVDC/Al) of 1 capsule.

Australian Register of Therapeutic Goods (ARTG)

AUST R 162766 - DIZOLE ONE Fluconazole 150mg capsule blister pack - (New formulation)

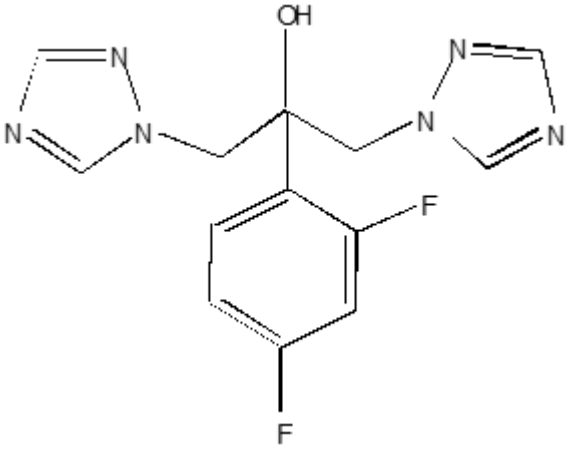
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical Structure



Chemical name

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

CAS Number

86386-73-4

Molecular formula

$C_{13}H_{12}F_2N_6O$

Molecular weight

306.3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

24/06/2009

10 DATE OF REVISION

05/01/2024

Summary Table of Changes

Section Changed	Summary of New Information
2	Minor editorial change
4.4	Addition of more restrictive safety-related information to Section 4.4
4.5	Addition of more restrictive safety-related information to Section 4.5
4.8	Addition of more restrictive safety-related information to Section 4.8
5.1	Additional information under Microbiology subheading

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