AUSTRALIAN PRODUCT INFORMATION – DIFLUCAN® (FLUCONAZOLE)

1. NAME OF THE MEDICINE

Fluconazole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIFLUCAN is available as:

Gelatin Capsules:

Gelatin capsules containing 50 mg, 100 mg, 150 mg or 200 mg fluconazole.

Solution for Injection

An intravenous infusion containing fluconazole 2 mg/mL in 0.9% saline solution. The pH of the solution is 4.0 - 8.0. Each 100 mL contains 15 mmol each of sodium and chloride.

Powder for Oral Suspension

A powder for oral suspension containing fluconazole 50 mg/5 mL.

Excipient(s) with known effect:

***Capsules*:** Lactose monohydrate

***Powder for oral suspension*:** Sodium benzoate and sucrose

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Hard Gelatin Capsules

50 mg light turquoise blue opaque cap and white opaque body, marked with the Pfizer logo and FLU-50.

100 mg standard blue opaque cap and white opaque body, marked with the Pfizer logo and FLU-100.

150 mg light turquoise blue opaque cap and body, marked with the Pfizer logo and FLU-150.

200 mg purple opaque cap and white opaque body, marked with the Pfizer logo and FLU-200

Solution for Injection

Vials containing 50 mL (100 mg) or 100 mL (200 mg).

Powder for Oral Suspension

35 mL bottle containing 50 mg/5 mL of orange flavoured suspension when reconstituted.

Not all presentations may be marketed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIFLUCAN, given orally, is indicated for:

- Treatment of cryptococcal meningitis in patients who are unable to tolerate amphotericin B.

  NOTE: Data suggest that the clinical efficacy of DIFLUCAN 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 AIDS.

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

- Secondary prophylaxis of oropharyngeal candidiasis in patients with HIV infection.

- Serious and life-threatening *Candida* infections in patients who are unable to tolerate amphotericin B.

  NOTE: It remains to be shown that DIFLUCAN 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 Section 4.8 Adverse effects (undesirable effects)).

DIFLUCAN IV is indicated for the same conditions in adults and children but should be used only when DIFLUCAN cannot be administered orally.

4.2 Dose and method of administration

Dosage

DIFLUCAN is normally administered orally. If oral administration is not possible, it may be administered by intravenous infusion at a rate not exceeding 200 mg/hour. 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 DIFLUCAN 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.

DIFLUCAN intravenous infusion is compatible with the following:

- Ringer's solution
- Normal saline

DIFLUCAN may be infused through an existing line with one of the above listed fluids. Although no specific incompatibilities have been noted, mixing with any other drug prior to infusion is not recommended.

Adults

- ***Cryptococcal meningitis in patients who are unable to take or tolerate amphotericin B***: The usual dose is 400 mg on the first day followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgement of the patient's response to therapy. Patients not responding to treatment for up to 60 days would appear unlikely to respond to DIFLUCAN.

  Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but should continue 10-12 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 AIDS patients:*** After the patient receives a full course of primary therapy, DIFLUCAN may be administered at a once daily dose of 100-200 mg.

- ***Oropharyngeal candidiasis:*** The recommended dose is 100 mg on the first day followed by 50 mg once daily. For the treatment of oesophageal candidiasis the recommended dose is 200 mg 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 infections:*** The recommended dose is 150 mg as a single dose once weekly.

- ***Serious and life-threatening candidal infections in patients unable to tolerate amphotericin B:*** A loading dose of 400 mg (up to 800 mg) is administered on the first day followed by 200 mg daily. Depending on the clinical response, the dose may be increased to 400 mg daily. Duration of treatment is based on clinical response; patients should be treated for minimum of 4 weeks and for at least 2 weeks following resolution of symptoms.

- ***Vaginal candidiasis when topical therapy has failed:*** DIFLUCAN 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).

- ***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 4 weeks.

Children

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

- ***Mucosal candidiasis:*** 3 mg/kg once daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady state levels more rapidly.

- ***Systemic candidiasis:*** refer to Table 1 for dosing regimens recommended for paediatric patients to achieve systemic exposures similar to adults, i.e., to maintain an AUC_{0-24} between 400-800 mg*h/L.

  Table 1: Recommended Dosing Regimens for the Treatment of Systemic *Candida* Infections in Paediatric Patients

Patient age	Dosing Regimen
3 months and older	A loading dose of 25 mg/kg on the first day (not to exceed 800 mg) followed by 12 mg/kg once daily (not to exceed 400 mg)
Birth to 3 months postnatal age and gestational age 30 weeks and above	25 mg/kg on the first day, followed by 12 mg/kg once daily
Birth to 3 months postnatal age and gestational age less than 30 weeks	25 mg/kg on the first day, followed by 9 mg/kg once daily

  Patients with systemic candidiasis should be treated for a minimum of 3 weeks and for at least 2 weeks following the resolution of symptoms. The duration of treatment should be guided by the adequacy of source control and clinical response.

- ***Cryptococcal infection:*** 6-12 mg/kg once 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.

Dosage adjustment

Elderly

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

Renal Impairment

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 follows:

Table 2: Recommended dosage interval and dose based on creatinine clearance

Creatinine Clearance (mL/min)	**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

Patients receiving haemodialysis: One recommended dose after every haemodialysis 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 following formula (based on sex, weight, and age of patient) should be used to estimate the creatinine clearance in mL/minute.

Males: $$\frac{\text{Weight (kg)} \times (140\text{-age}) \times 0.0885}{72 \times \text{serum creatinine (mmol/L)}}$$

Females: $0.85 \times$ above value

Method of administration

DIFLUCAN may be administered either orally (as capsules or powder for oral suspension), or by intravenous infusion (Solution for Infusion) if it cannot be administered orally. The powder is intended for reconstitution as a suspension for oral use only. Under no circumstances should it be given as an intravenous infusion. DIFLUCAN infusion has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of DIFLUCAN should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion (see Section 6.2 Incompatibilities).

If DIFLUCAN infusion is administered to patients requiring sodium or fluid restriction, consideration should be given to the salt content of the infusion fluid (15 mmol/100 mL) and the total volume of fluid administered.

DIFLUCAN infusions are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Do not use if the solution is cloudy or precipitated or if the seal is not intact.

4.3 Contraindications

DIFLUCAN should not be used 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/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, 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).

4.4 Special warnings and precautions for use

In rare cases, as with other azoles, anaphylaxis has been reported. Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with DIFLUCAN. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. 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, DIFLUCAN should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and DIFLUCAN discontinued if bullous lesions or erythema multiforme develop (see Section 4.8 Adverse effects (undesirable effects)).

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 hypokalaemia 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)).

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 metabolised through CYP2C9, CYP2C19 and CYP3A4 should be monitored (see Section 4.5 Interactions with other medicines and other forms of interactions).

Adrenal insufficiency has been reported in patients receiving other azoles (e.g., ketoconazole).

Cases of adrenal insufficiency were reported in patients receiving fluconazole.

DIFLUCAN 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.

DIFLUCAN powder for oral suspension contains sucrose and should not be used in patients with hereditary fructose, glucose/galactose malabsorption and sucrase-isomaltase deficiency.

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, prescribers 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 hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed.

Patients who develop abnormal liver function tests during DIFLUCAN therapy should be monitored for the development of more severe hepatic injury. DIFLUCAN should be discontinued 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

Dosage should be adjusted for elderly patients with renal impairment (see Section 4.2 Dose and method of administration).

Paediatric use

See Section 4.2 Dose and method of administration – Dosage – Children, and Section 5.2 Pharmacokinetic properties - Children.

Effects on laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interactions

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 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, ciclosporin, hydrochlorothiazide, oral hypoglycaemics, phenytoin, rifampicin, rifabutin, tacrolimus and theophylline. These are described in greater detail below.

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 100 mg DIFLUCAN and 50 mg hydrochlorothiazide for 10 days in normal volunteers resulted in an increase of 41% in C_{max} and an increase of 43% in area under the concentration versus time curve (AUC) of fluconazole, compared to DIFLUCAN given alone. Overall, the plasma concentrations of fluconazole were approximately 3.26 - 6.52 µmol/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 200 mg dose of DIFLUCAN 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 DIFLUCAN does not appear to be affected by agents that increase gastric pH. Single dose administration of DIFLUCAN (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 DIFLUCAN (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) 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 metabolised 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).

Abrocitinib: Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If coadministered with fluconazole, adjust the dose of abrocitinib as instructed in the abrocitinib Product Information.

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.

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 1 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 *Candida albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two drugs in systemic infection with *Aspergillus 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 torsade 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 coadministration of fluconazole and cisapride is contraindicated (see Section 4.3 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/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/day with terfenadine should be carefully monitored (see Section 4.3 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 Section 4.3 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 Section 4.3 Contraindications).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and quinidine is contraindicated.

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

Concomitant use that should be avoided or used with caution:

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).

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.

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

Anticoagulants: Careful monitoring of prothrombin time in patients receiving fluconazole and indanedione anticoagulants is recommended.

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} by 20% to 32% and increases the half-life by 25% to 50% due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

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.

Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolised 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.

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. This combination may be used by reducing the dosage of ciclosporin depending on ciclosporin 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.

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

Fentanyl: One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomised crossover study with 12 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 (dose-dependent) when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine 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.

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*:* Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other non-steroidal anti-inflammatory drugs (NSAIDs) that are metabolised 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.

Olaparib*:* Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, reduce the dose of olaparib as instructed in the Olaparib Prescribing Information.

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 3-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 the 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.

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 100 mg of DIFLUCAN as a single daily oral dose for 7 days. DIFLUCAN 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.

***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 dose theophylline or who are otherwise at increased risk of theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and therapy modified appropriately if signs of toxicity develop.

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

Tolvaptan: Exposure to tolvaptan is significantly increased (200% in AUC; 80% in C_{max}) when tolvaptan, a CYP3A4 substrate, is coadministered 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.

***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, central nervous system (CNS) related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

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

***Warfarin**:* A single dose of warfarin (15 mg) given to normal volunteers, following 14 days of orally administered DIFLUCAN (200 mg) resulted in a 12% increase in the prothrombin time response (area under the prothrombin time-time curve). One of 13 subjects experienced a 2-fold increase in his prothrombin time response. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melena) 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 the 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.

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 DIFLUCAN 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of 50 mg of DIFLUCAN. The mean increase in ethinyl estradiol 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 DIFLUCAN tablets or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving DIFLUCAN during one cycle and placebo during the other. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (Day 10) of both cycles. Following administration of 200 mg of DIFLUCAN, the mean percentage increase in AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyl estradiol 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 DIFLUCAN and single doses of ethinyl estradiol 35 microgram and norethisterone 0.5 mg. AUC of ethinyl estradiol was increase by 24% (range: 3 to 59%) and AUC of norethindrone was increased by 13% (range: -5 to 36%).

Multiple doses of DIFLUCAN 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 crossover 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%.

Table 3: 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] Ciclosporin[4] Oral hypoglycaemics[3] Phenytoin[4] Rifabutin[5]	Antacids Azithromycin Cimetidine Oral contraceptives

		Tacrolimus[5] Theophylline[5] Coumarin-type or indanedione anticoagulants[6] Zidovudine[5] Ibrutinib[5] Olaparib Tolvaptan[5]	

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

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 mg/kg, 10 mg/kg or 20 mg/kg or with parenteral doses of 5 mg/kg, 25 mg/kg or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5 mg/kg, 20 mg/kg and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see Section 5.1 Pharmacodynamic properties).

Use in pregnancy – 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.

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 fetus.

Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.

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.

In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.

There are no adequate and well-controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 mg/day to 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Adverse fetal 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.

Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high-dose (400 mg/day to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

Use in lactation

Fluconazole has been found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended. The elimination half-life from breast milk approximates the plasma elimination half-life of 30 hours. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 mL/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DIFLUCAN and any potential adverse effects on the breast-fed child from DIFLUCAN or from the underlying maternal condition.

A pharmacokinetic study in 10 lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of DIFLUCAN. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose.

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)

Adults

Summary of safety profile

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).

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.

1. Multiple daily dosing for treatment of oral and for oral and oropharyngeal candidiasis; cryptococcal meningitis; or systemic candidiasis.

DIFLUCAN is generally well tolerated. Sixteen percent of over 4000 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 disorders. 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 Section 4.4 Special warnings and precautions for use). There have been rare cases of serious hepatic reactions during treatment with DIFLUCAN (see Section 4.4 Special warnings and precautions for use). 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 DIFLUCAN.

In two comparative trials evaluating the efficacy of DIFLUCAN for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) 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 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in the pre-marketing 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 DIFLUCAN concomitantly with one or more of the following

medications; rifampicin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycaemic agents.

Other adverse reactions observed include the following:

Table 4: Observed adverse reactions

MedDRA System Organ Class Frequency*	**Adverse Drug Reactions**
Blood and lymphatic system disorders	
Rare	Leukopenia (including neutropenia and agranulocytosis), thrombocytopenia
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal pain, diarrhoea
Immune system disorders	
Rare	Anaphylaxis, angioedema
Metabolism and nutrition disorders	
Rare	Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia
Nervous system disorders	
Common	Headache
Uncommon	Seizures, dizziness, paraesthesia, taste perversion
Rare	Tremor
Skin and subcutaneous tissue disorders	
Common	Rash
Rare	Angioedema, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis (see Section 4.4 Special warnings and precautions for use), alopecia

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

Table 5: Observed adverse reactions after single 150 mg dose for vaginal candidiasis

MedDRA System Organ Class Frequency*	**Adverse Drug Reaction**
Eye disorders	
Uncommon	Abnormal vision
Gastrointestinal disorders	
Common	Nausea, abdominal pain, diarrhoea, dyspepsia
Uncommon	Constipation, flatulence, vomiting, loose stools, dry mouth
General disorders and administration site conditions	

MedDRA System Organ Class Frequency*	**Adverse Drug Reaction**
Uncommon	Thirst, fatigue, malaise, pain, rigors, asthenia, fever
Infections and infestations	
Uncommon	Pharyngitis, herpes simplex
Metabolism and nutrition disorders	
Uncommon	Anorexia
Musculoskeletal and connective tissue disorders	
Uncommon	Back pain, myalgia
Nervous system disorders	
Common	Headache
Uncommon	Dizziness, vertigo, hyperkinesia, hypertonia, taste perversion, visual field defect
Psychiatric disorders	
Uncommon	Insomnia, nervousness
Renal and urinary disorders	
Uncommon	Polyuria, renal pain
Reproductive system and breast disorders	
Uncommon	Intermenstrual bleeding, dysmenorrhoea, leukorrhoea, menorrhagia, uterine spasm, vaginal disorders, female sexual dysfunction
Skin and subcutaneous tissue disorders	
Uncommon	Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria
Vascular disorders	
Uncommon	Flushing, hot flushes
Hepatobiliary disorders	
Common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
Uncommon	Cholestasis, jaundice, bilirubin increased
Rare	Hepatic toxicity, including rare cases of fatalities. Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage
Cardiac disorders	
Rare	Torsades de pointes, QT prolongation

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

Table 6: Observed adverse reactions with patients treated with 150 mg weekly in dermal therapeutic studies

MedDRA System Organ Class Frequency*	Adverse Drug Reactions
Gastrointestinal disorders	
Common	Abdominal pain, dyspepsia
Investigations	
Uncommon	Elevation of transaminase >2-3 × upper limit of normal
Nervous system disorders	
Common	Headache
Uncommon	Paraesthesia
Psychiatric disorders	
Uncommon	Insomnia, somnolence
Skin and subcutaneous tissue disorders	
Uncommon	Pruritus, urticaria, increased sweating, drug eruption (including fixed drug eruption).

*Frequencies are categorised as follows: very common ≥10%; common from ≥1% to <10%; uncommon from ≥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 12 mg/kg/day, for up to 129 days. The majority of patients (n=522) received 2 to 8 mg/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:

Table 7: Adverse events in paediatric patients considered related to treatment

MedDRA System Organ Class Frequency*	Adverse Drug Reactions
Cardiac disorders	
Uncommon	Cardiomyopathy
Ear and labyrinth disorders	
Uncommon	Deafness
Gastrointestinal disorders	
Common	Vomiting, diarrhoea, abdominal pain
Uncommon	Nausea, dyspepsia, ileus, stomatitis, loose stools
Hepatobiliary disorders	
Uncommon	Hepatocellular damage, jaundice
Metabolism and nutrition disorders	
Uncommon	Anorexia
Nervous system disorders	

MedDRA System Organ Class Frequency*	**Adverse Drug Reactions**
Uncommon	Headache, taste perversion
Respiratory, thoracic and mediastinal disorders	
Uncommon	Hypoxia, respiratory disorder
Skin and subcutaneous tissue disorders	
Uncommon	Rash (erythematous & maculo-papular), pruritus, purpura
Vascular disorders	
Uncommon	Hypertension

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

Post-marketing experience

In addition, the following adverse events have occurred during post-marketing:

Table 8: Adverse events reported post-marketing

Cardiac disorders	Torsade de pointes (see Section 4.4 Special warnings and precautions for use)
Gastrointestinal disorders	Dyspepsia, vomiting
Hepatobiliary disorders	Hepatocellular necrosis
Immune system disorders	Anaphylaxis (including face oedema, angioedema and pruritus)
Investigations	QT prolongation (see Section 4.4 Special warnings and precautions for use)
Metabolism and nutrition disorders	Hypercholesterolaemia, hypertriglyceridaemia and hypokalaemia
Nervous system disorders	Dizziness
Skin and subcutaneous tissue disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS)

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

The minimal lethal human dose has been not established. There have been reports of overdosage with DIFLUCAN, and in one case, a 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after

reportedly ingesting 8,200 mg of DIFLUCAN. 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 Section 4.8 Adverse effects (undesirable 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%.

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 P-450 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 adrenocorticotropic hormone (ACTH) stimulated response in healthy female volunteers. Plasma estradiol 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.

Susceptibility *in vitro*

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

Pharmacokinetic/pharmacodynamic relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and

to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanisms of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high MICs to fluconazole which impacts adversely efficacy *in vivo* and clinically.

In usually susceptible species of *Candida,* the most commonly encountered mechanism of resistance development involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutation, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways.

There have been reports of superinfection with Candida species other than *C. albicans*, which often have inherently reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g., *C. krusei, C. auris*). Such infections may require alternative antifungal therapy. The resistance mechanisms have not been completely elucidated in some intrinsically resistant (*C. krusei*) or emerging (*C. auris*) species of Candida.

Susceptibility testing breakpoints

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rationale document (2020)-version 3; European Committee on Antimicrobial Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs, Version 10.0, valid from 2020-02-04). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Table 9: Breakpoints for fluconazole for *Candida* species

Antifungal	**Species-related breakpoints (S≤/R>) in mg/L**						**Non-species related breakpoints[A] S≤/R> in mg/L**
	Candida albicans	*Candida dubliniensis*	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*	*Candida tropicalis*	
Fluconazole	2/4	2/4	0.001*/16	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

* = The entire *C. glabrata* is in the I category. MICs against *C. glabrata* should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. I - Susceptible, increased exposure: A microorganism is categorised as

Susceptible, increased exposure when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

For the most recent susceptibility testing interpretation according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), Antifungal agents, please see (https://www.eucast.org/).

Clinical Trials

No data available

5.2 Pharmacokinetic properties

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 20-50 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 (11-12%).

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

Table 10: Tissue to plasma concentration for various tissues or fluids

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 DIFLUCAN 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, 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 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 2 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:

Table 11: Pharmacokinetic data in children

Age	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (Hours)	C_{max} (mcg/mL)	AUC (mcg*h/mL)	Vdss (L/kg)
2 days to 60 days	Multiple IV: 25 mg/kg loading dose on Day 1 followed by 12 mg/kg once daily	0.29	54.2	23.4	439	1.13
9 months to 13 years	Single oral: 2 mg/kg	0.40	25.0	2.9	94.7	-
9 months to 13 years	Single oral: 8 mg/kg	0.51	19.5	9.8	362.5	-
5 years to 15 years	Multiple IV: 2 mg/kg	0.49	17.4	5.5	67.4	0.722
5 years to 15 years	Multiple IV: 4 mg/kg	0.59	15.2	11.4	139.1	0.729
5 years to 15 years	Multiple IV: 8 mg/kg	0.66	17.6	14.1	196.7	1.069

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

In premature newborns (gestational age 26 to 29 weeks), the mean clearance within 36 hours of birth was 0.180 mL/min/kg, which increased with time to a mean of 0.218 mL/min/kg 6 days later and 0.333 mL/min/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours 6 days later and 46.6 hours 12 days later.

In a study of 13 paediatric patients (preterm and term infants with median gestational age (GA) of 37 weeks, GA range: 24 to 39 weeks; median postnatal age (PNA) of 19 days, PNA range: 5 to 262 days) 12 infants received a 25 mg/kg loading dose, and 9/12 (75%) achieved an AUC_{0-24} of >400 mg*h/L in the first 24 hours. A population pharmacokinetic model using data from 55 paediatric patients (GA of 23 to 40 weeks, PNA of 1 to 88 days) found that a loading

dose of 25 mg/kg is necessary to reach target AUC >400 mg*h/L within 24 hours of initiating therapy in paediatric patients younger than 3 months of age. A maintenance dose of 9 mg/kg daily should be used in paediatric patients born at GA less than 30 weeks and 12 mg/kg daily in paediatric patients with GA equal or greater than 30 weeks (see Section 4.2 Dose and method of administration).

A population PK model using data from 21 paediatric patients ages from birth to 17 years supported with extracorporeal membrane oxygenation (ECMO), and 19 paediatric non-ECMO patients ages from birth to 2 years found that clearance was related to serum creatinine while a higher volume of distribution was related to presence of ECMO support. The median volume of distribution was 1.3 L/kg in paediatric patients on ECMO and 0.9 L/kg in those not on ECMO. Simulations suggested that a loading dose of 35 mg/kg is needed to achieve the target AUC_{0-24} >400 mg*h/L within the first 24 hours in paediatric patients on ECMO (see Section 4.2 Dose and method of administration).

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* spp. Activity has been demonstrated *in vivo* in normal and immunocompromised animals against infections with *Candida* spp, including systemic candidiasis and in normal animals with *C. neoformans*, including intracranial infections. One case of cross-resistance of *Candida* to fluconazole in a patient (non-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.

5.3 Preclinical safety data

Genotoxicity

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 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 mg/kg/day, 5 mg/kg/day or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 mg/kg/day and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DIFLUCAN Gelatin capsules: Gelatin capsules contain the following inactive ingredients - gelatin, lactose monohydrate, maize starch, colloidal anhydrous silica, magnesium stearate, sodium lauryl sulfate, titanium dioxide, (50, 100 and 150 mg capsules only), patent blue V (50, 100 and 150 mg capsules only), erythrosine (100 and 200 mg capsules only) and indigo carmine (200 mg capsules only).

DIFLUCAN Solution for Injection: An intravenous infusion containing 0.9% saline solution. Each 100 mL contains 15 mmol each of sodium and chloride.

DIFLUCAN Oral suspension: A powder for oral suspension containing the following inactive ingredients - sucrose, colloidal anhydrous silica, xanthan gum, sodium citrate dihydrate, citric acid, sodium benzoate, titanium dioxide and natural orange flavour 57458 AP0551.

6.2 Incompatibilities

Although no specific incompatibilities have been noted, mixing with any other drug prior to infusion is not recommended (see Section 4.2 Dose and method of administration).

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

Capsules:	Store below 30°C.
Solution for injection:	Store below 30°C.
Powder for oral suspension:	Store below 30°C.

6.5 Nature and contents of container

Hard gelatin capsules

50 mg - blister packs of 28.

100 mg - blister packs of 28.

150 mg - blister packs of 1.

200 mg - blister packs of 28.

Solution for injection

Vials contain 50 mL (100 mg) or 100 mL (200 mg).

Powder for oral suspension

35 mL (after reconstitution) in high density polyethylene (HDPE) bottle.

Not all presentations may be marketed.

6.6 Special precautions for disposal

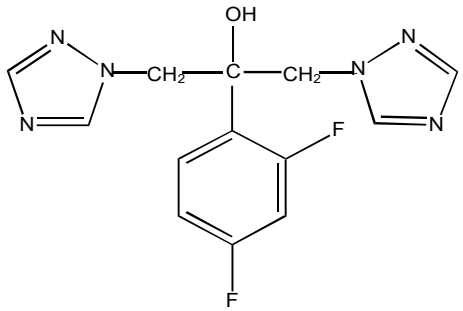
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

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

Chemical structure

Fluconazole is a bis-triazole with the following structural formula:



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

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

Molecular Weight: 306.3.

CAS number

86386-73-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street

Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

14 August 1991

10. DATE OF REVISION

02 December 2025

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
Throughout	Minor editorial changes.
4.2	Update to paediatric dosing information for systemic candidiasis
5.2	Include additional information on paediatric population based on data PK study