1 PRODUCT NAME

Fluconazole-Baxter 0.2% w/v (2 mg/mL) solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluconazole-Baxter, solution for infusion contains 2 mg fluconazole per mL.

Each 50 mL vial of solution for infusion contains 100 mg fluconazole.
Each 100 mL vial of solution for infusion contains 200 mg fluconazole.
Each 200 mL vial of solution for infusion contains 400 mg fluconazole.

Excipient(s) with known effect
Each mL contains 9 mg sodium chloride (equivalent to 0.154 mmol sodium) (see section 4.4).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Fluconazole-Baxter injection for intravenous infusion is a clear colourless solution.
The pH of the solution is 4.0 - 8.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole-Baxter intravenous solution for infusion should be used only when fluconazole cannot be administered orally.

Fluconazole-Baxter is indicated for the treatment of the following conditions:

- Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g., pulmonary, cutaneous). Normal hosts, and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. **Fluconazole-Baxter** can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.
- Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infection including infections of the peritoneum, endocardium and pulmonary and urinary tracts. Patients with malignancy, in intensive care units, receiving cytotoxic or immunosuppressive therapy, or with other factors predisposing to candidal infection may be treated.
- Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated.
- Vaginal candidiasis, acute or recurrent.
- Prevention of fungal infection in immunocompromised patients considered at risk as a consequence of HIV infections or neutropenia following cytotoxic chemotherapy, radiotherapy or bone marrow transplant.

4.2 Dose and method of administration

Dose
Fluconazole is normally administered orally. If oral administration is not possible, it may be administered by intravenous infusion (see *Method of Administration* below for rate of infusion).

The daily dose of **Fluconazole-Baxter** should be based on the infecting organism, severity of the fungal infection and the patient's response to therapy. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections requiring multiple dose 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 usually require maintenance therapy to prevent relapse.

Adults

Cryptococcal meningitis and cryptococcal infections at other sites
The usual dose is 400mg on the first day followed by 200 to 400mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6 - 8 weeks for cryptococcal meningitis.

Prevention of relapse of cryptococcal meningitis in AIDS patients
After the patient receives a full course of primary therapy, **Fluconazole-Baxter** may be administered indefinitely at a once daily dose of 200mg.

Candidaemia, disseminated candidiasis and other invasive candidal infections
The usual dose is 400mg on the first day followed by 200mg once daily. Depending on the clinical response, the dose may be increased to 400mg once daily. Duration of treatment is based upon the clinical response.

Oropharyngeal candidiasis
The usual dose is 50mg once daily for 7 - 14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function. For atrophic oral candidiasis associated with dentures the usual dose is 50mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.

Other candidal infections of mucosa (except vaginal candidiasis, see below), e.g., oesophagitis, candiduria, mucocutaneous candidiasis etc.
The usual effective dose is 50mg once daily, given for 14 - 30 days.
In unusually difficult cases of mucosal candidal infections the dose may be increased to 100mg daily.

Vaginal candidiasis when topical therapy has failed
Fluconazole-Baxter 150mg should be administered as a single dose.

Prevention of fungal infections in immunocompromised patients
The dose should be 50mg once daily while the patient is at risk as a consequence of receiving cytotoxic chemotherapy, radiotherapy or bone marrow transplant. A higher dose of 100mg/day may be used in patients at risk of severe recurrent infections.

Dermatomycoses
The usual dosage is 50mg once daily or 150mg once weekly for two to four weeks. Tinea pedis may require treatment for up to six weeks.

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

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

Systemic candidiasis and cryptococcal infection
6 - 12mg/kg once daily, depending on the severity of the disease.

Prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy
3 - 12mg/kg once daily, depending on the extent and duration of the induced neutropenia (see adult dosing).

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

Method of administration
Fluconazole-Baxter may be administered by intravenous infusion at a rate not exceeding 200 mg/hour, given as a constant infusion. Fluconazole infusion has been used safely for up to 14 days of intravenous therapy. 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.*

For instructions on dilution of the medicine before administration, see section 6.6.

Dosage adjustments
Elderly
Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance < 50mL/min) the dosage schedule should be adjusted as described below.

Adult patients with renal impairment
Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single dose therapy are necessary.

In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50mg to 400mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance (mL/min)	**Percent of Recommended Dose**
> 50	100%
11 - 50	50%
Patients receiving haemodialysis	One dose after every haemodialysis session.

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 x above value

Paediatrics with renal impairment

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

4.3 Contraindications

Fluconazole-Baxter infusion solution should not be used in patients with known sensitivity to fluconazole, to related azole compounds, or to any of its excipients.

Co-administration 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. 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 sections 4.4 and 4.5).

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 fluconazole. 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, fluconazole should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop (see section 4.8).

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).

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 *torsade de pointes*. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions (see section 4.8).

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).

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

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 fluconazole therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see section 4.8).

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).

Paediatric use
See sections 4.2 and 5.2.

Effects on laboratory tests
No data available.

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).

If **Fluconazole-Baxter** infusion is administered to patients requiring sodium or fluid restriction, consideration should be given to the salt content of the infusion fluid (7.54mmol/50mL) and the total volume of fluid administered.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions
Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP2C and to a lesser extent the CYP3A isoforms. Co-administration of fluconazole with 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 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 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 fluconazole 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 fluconazole 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 fluconazole after chronic rifampicin administration resulted in a 25% decrease in AUC and a 20% shorter half-life of fluconazole in normal volunteers. Depending on clinical circumstances, an increase of the dose of fluconazole should be considered when it is administered with rifampicin.

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

Gastrointestinal drugs

In fasted normal volunteers, absorption of orally administered fluconazole does not appear to be affected by agents that increase gastric pH. Single dose administration of fluconazole (100 mg) with cimetidine (400 mg) resulted in a 13% reduction in AUC and a 21% reduction in C_{max} of fluconazole. Administration of an antacid containing aluminium and magnesium hydroxides immediately prior to a single dose of fluconazole (100 mg) had no effect on the absorption or elimination of fluconazole.

Effects of fluconazole on other medicinal products

As 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 co-administered with fluconazole. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4 to 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Abrocitinib

Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If co-administered with fluconazole, adjust the dose of abrocitinib as instructed in the abrocitinib prescribing 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 a day) 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 co-administration of fluconazole and cisapride is contraindicated (see section 4.3).

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 co-administration of fluconazole at doses lower than 400 mg/day with terfenadine should be carefully monitored (see section 4.3).

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).

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).

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*. Co-administration 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. Co-administration 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} with 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 cyclosporin. 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 co-administered 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)
Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-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.

Oral hypoglycaemic agent
The effects of fluconazole on the pharmacokinetics of the sulphonylurea oral hypoglycaemic agents tolbutamide, glipizide and glibenclamide were examined in three placebo-controlled crossover studies in normal volunteers. All subjects received the sulphonylurea alone and following treatment with 100 mg of fluconazole as a single daily oral dose for 7 days. Fluconazole administration resulted in significant increases in C_{max} and AUC of the sulphonylurea. Several subjects in these three studies experienced symptoms consistent with hypoglycaemia. In the glibenclamide study, several volunteers required oral glucose treatment. When fluconazole and sulphonylureas are co-administered, blood glucose concentrations should be monitored carefully and the dose of the sulphonylurea adjusted accordingly.

Phenytoin
Fluconazole inhibits the hepatic metabolism of phenytoin. With co-administration, 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 co-administered. 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. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage are 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.

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 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 C_{max}) 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.

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 fluconazole (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 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 the $_{Cmax}$ 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 fluconazole 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 fluconazole. 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 fluconazole tablets or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving fluconazole during one cycle and placebo during the other. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (day 10) of both cycles. Following administration of 200 mg of fluconazole, the mean percentage increase in AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for 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 fluconazole and single doses of ethinyl estradiol 35 microgram and norethindrone 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 fluconazole may increase exposure to hormone levels in women taking oral contraceptives and are unlikely to result in decreased efficacy of the oral contraceptive.

Two-way Interactions

Minor or no significant pharmacokinetic interactions that require no dosage adjustment

Azithromycin

An open-label, randomised, three-way 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 co-administered with azithromycin to fluconazole administered alone was 101%. The estimated ratio of the mean AUC of azithromycin co-administered with fluconazole to azithromycin administered alone was 107%. The estimated ratio of the mean C_{max} of fluconazole co-administered with azithromycin to fluconazole administered alone was 104%. The estimated ratio of the mean C_{max} of azithromycin co-administered with fluconazole to azithromycin administered alone was 82%.

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] Tacrolimus[5] Theophylline[5] Coumarin-type or indanedione anticoagulants[6] Zidovudine[5] Ibrutinib[5] Olaparib Tolvaptan[5]	Antacids Azithromycin Cimetidine Oral Contraceptives

1. Fluconazole blood levels increased
2. Fluconazole blood levels decreased
3. Carefully monitor blood glucose levels
4. Carefully monitor plasma drug levels
5. Carefully monitor patients for signs of toxicity or adverse events
6. Carefully monitor patient's prothrombin time

4.6 Fertility, pregnancy and lactation

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 by mouth. 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).

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 foetal 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 foetus.

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 is an increased risk of spontaneous abortion in women treated with fluconazole. Doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.

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 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 foetal effects have been seen in animals only at high dose levels associated with maternal toxicity. These findings are not considered relevant to fluconazole used at therapeutic doses.

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.

Breast-feeding

Fluconazole is 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 fluconazole and any potential adverse effects on the breastfed child from fluconazole 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 fluconazole. 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 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).

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

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

Fluconazole 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). There have been rare cases of serious hepatic reactions during treatment with fluconazole (see section 4.4). Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. In addition, transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of fluconazole.

In two comparative trials evaluating the efficacy of fluconazole for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (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 fluconazole concomitantly with one or more of the following medications; rifampicin, phenytoin, isoniazid, valproic acid, or oral sulphonylurea hypoglycaemic agents.

Other adverse reactions observed included the following:

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	Tremors
Skin and subcutaneous tissue disorders	
Common	Rash
Rare	Angioedema, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis (see section 4.4), 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%.	

Single 150mg oral dose for vaginal candidiasis

MedDRA System Organ Class Frequency*	**Adverse Drug Reactions**
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	
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 disorder, female sexual dysfunction
Skin and subcutaneous tissues 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	*Torsade 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%.	

Patients treated with 150mg weekly in dermal therapeutic studies

MedDRA System Organ Class Frequency*	**Adverse Drug Reactions**
Gastrointestinal disorders	
Common	Abdominal pain, dyspepsia
Investigations	
Unommon	Elevation of transaminase > 2 - 3 x upper limit of normal
Nervous system disorders	
Common	Headache
Uncommon	Paraesthesia
Psychiatric disorders	
Uncommon	Insomnia, somnolence
Skin and subcutaneous tissues 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%.	

Paediatrics/Children

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

MedDRA System Organ Class 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	
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:

Cardiac disorders	*Torsade de pointes* (see section 4.4)
Gastrointestinal disorders	Dyspepsia, vomiting
Hepatobiliary disorders	Hepatocellular necrosis
Immune system disorders	Anaphylaxis (including face oedema, angioedema and pruritus)
Investigations	QT prolongation (see section 4.3).
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 of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose
The minimal lethal human dose has not been established. There have been case reports of overdosage with fluconazole and in one case, a 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to hospital, and his condition resolved within 48 hours.

Signs and symptoms are likely to be an extension of those under section 4.8.

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 risk assessment and advice on the management of overdose please contact the National Poisons Centre on: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group
Antiinfectives for systemic use, Antimycotics for systemic use, triazole derivatives.

ATC code
J02AC01.

Mechanism of action
Fluconazole, a member of a new class triazole of antifungal agents, is a potent and specific inhibitor of fungal sterol synthesis.

Intravenously administered fluconazole is active in a variety of animal fungal infection models. Activity has been demonstrated against opportunistic mycoses, such as infections with *Candida spp*, including systemic candidiasis and in immunocompromised animals; with *Cryptococcus neoformans*, including intracranial infections, with *Microsporum spp*; and with *Trichophyton spp*. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitidis*; with *Coccidioides immitis*, including intracranial infection; and with *Histoplasma capsulatum* in normal and immunosuppressed animals. 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.

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 50mg 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 (I) to fluconazole while *C. krusei* is intrinsically resistant to fluconazole. The MICs and epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans*. The recently emerging species *C. auris* tends to be relatively resistant to fluconazole.

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 minimum inhibitory concentration (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 minimum inhibitory concentrations (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 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

Susceptibility testing interpretation according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), Antifungal agents is recommended (https://www.eucast.org/).

Further information

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

Chemical name: 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol

Molecular weight: 306.277g/mol.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route.

Absorption

After oral administration fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4 - 5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state level by day 2.

Distribution

The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11 - 12%).

Fluconazole achieves good penetration into all body fluids studied. See table below.

Tissue or Fluid	**Tissue (Fluid) : Plasma Concentration***
Cerebrospinal fluid+	0.5 - 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Blister skin	2
* Relative to concurrent concentrations in plasma in subjects with normal renal function + Independent of degree of meningeal inflammation	

Biotransformation

Fluconazole is metabolised only to a minor extent. About 11% of the dose is excreted in the urine as metabolites.

Elimination

The major route of excretion is renal with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites. The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of fluconazole may need to be reduced in patients with impaired renal function (see section 4.2). 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 in the treatment of all other indicated fungal infections.

Special population: Paediatrics

There are differences in the pharmacokinetics of fluconazole between adults and children, with children after the neonatal period, generally having a faster elimination rate and larger volume of distribution than in adults. These differences result in less accumulation on multiple dosing in children, with steady-state achieved faster than in adults. Neonates have reduced elimination rates relative to

adults and even higher volumes of distribution in comparison with older children. During the first 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 are 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:

Age	**Dose (mg/kg)**	**Clearance (mL/min/kg)**	**Half-life (hours)**	**C_{max} (µg/mL)**	**V_{dss} (L/kg)**
9 months – 13 years Single oral					
	2 mg/kg	0.40	25.0	2.9	-
	8 mg/kg	0.51	19.5	9.8	-
5 – 15 years Multiple I.V.					
	2 mg/kg	0.49	17.4	5.5	0.722
	4 mg/kg	0.59	15.2	11.4	0.729
	8 mg/kg	0.66	17.6	14.1	1.069

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

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 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

Hydrochloric acid q.s.
Sodium chloride
Water for injections q.s. to 1mL.

6.2 Incompatibilities

Fluconazole-Baxter must not be mixed with other medicinal products except those mentioned in (see section 6.6 and as instructed in section 4.2.

6.3 Shelf life

36 months. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store at or below 30°C. Protect from light. Do not refrigerate.

Once opened the product should be used immediately. Any unused infusion should be discarded.

From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.5 Nature and contents of container

Fluconazole-Baxter 2mg/mL is a clear, colourless infusion solution containing 2 mg fluconazole per mL.

Fluconazole-Baxter is available in the following bottle sizes:

- 100 mg/50 mL: Packs of one bottle and packs of six bottles,
- 200 mg/100 mL Packs of one bottle, and
- 400 mg/200 mL: Packs of one bottle.

Not all pack sizes or presentations may be available.

6.6 Special precautions for disposal and other handling

Intravenous administration

If **Fluconazole-Baxter** infusion is administered to patients requiring sodium or fluid restriction, consideration should be given to the salt content of the infusion fluid (7.54mmol/50mL or 15.4mmol/100mL) and the total volume of fluid administered.

Fluconazole-Baxter infusion is intended only for intravenous administration using sterile equipment.

Fluconazole-Baxter intravenous infusion is compatible with the following:

- Ringer's solution
- Normal saline
- Dextrose 20%
- Hartmann's solution
- Potassium chloride in dextrose
- Sodium bicarbonate 4.2%
- Aminofusin.

Fluconazole-Baxter 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.

Fluconazole is for single use in one patient only. Discard any residue.

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.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription only medicine.

8 SPONSOR

Fluconazole-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
22 July 2010.

10 DATE OF REVISION OF THE TEXT

23 September 2025

SUMMARY TABLE OF CHANGES

All	Editorial changes.
3	Dose form and route of administration included.
4.3	New headings: Use in hepatic impairment and Use in renal impairment, (Use in elderly, Paediatric use, and Effects on laboratory tests.
4.5	Updated information and new interaction data relating to abrocitinib, everolimus. Guidance on clinical management of drug interactions table included
4.6	Breastfeeding: use in nursing mothers is not recommended.
4.7	Section aligned with text from source document.
4.8	ADR tables reformatted. Reporting adverse reactions url updated.
4.9	Updated risk assessment wording.
5.3	Text relocated.
6.3	Reference to packaging for expiry date.
6.5	Section updated.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.