

New Zealand Data Sheet



1. PRODUCT NAME

Ozole Capsule 50 mg
Ozole Capsule 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Ozole 50 mg capsule contains 50 mg of fluconazole.
Each Ozole 200 mg capsule contains 200 mg of fluconazole.

Excipient(s) with known effect

Ozole 50 mg and 200 mg capsules contain lactose monohydrate. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ozole 50 mg is available as a size 4 hard gelatin capsule with an opaque blue cap and opaque white body. The Capsule is printed Ranbaxy on both cap and body.

Ozole 200 mg is available as a size 0 hard gelatin capsule with a purple opaque cap and white opaque body. The Capsule is printed Ranbaxy on both cap and body.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

OZOLE is indicated for the treatment of the following conditions:

1. 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. OZOLE can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.
2. 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.

3. 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.
4. Vaginal candidiasis, acute or recurrent.
5. 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.
6. OZOLE 50 mg & 150 mg capsules are also indicated for the treatment of dermatomycoses including tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor & candidiasis.

4.2. Dose and method of administration

The daily dose of fluconazole should be based on the infecting organism and severity of the fungal infection and 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.

Dose

Adults

1. a) For cryptococcal meningitis and cryptococcal infections at other sites: The usual dose is 400 mg on the first day followed by 200 to 400 mg 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.

b) For prevention of relapse of cryptococcal meningitis in AIDS patients: After the patient receives a full course of primary therapy, fluconazole may be administered indefinitely at a single daily dose of 200 mg.
2. For candidaemia, disseminated candidiasis and other invasive candidal infections: The usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response, the dose may be increased to 400 mg once daily. Duration of treatment is based upon the clinical response.

3. For oropharyngeal candidiasis: The usual dose is 50 mg 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 50 mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.
4. For other candida infections of mucosa (except vaginal candidiasis, see below), e.g. oesophagitis, candiduria, mucocutaneous candidiasis etc.: the usual effective dose is 50 mg daily, given for 14-30 days.

In unusually difficult cases of mucosal candida infections the dose may be increased to 100 mg daily.

5. For vaginal candidiasis: OZOLE 150 mg should be administered as a single oral dose.

Median time to onset of symptom relief following a 150 mg single oral dose for the treatment of vaginal candidiasis is one day. The range of time to onset of symptom relief is one hour to nine days.

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

1. 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.
2. Systemic candidiasis and cryptococcal infection: 6-12 mg/kg once daily, depending on the severity of the disease.
3. Prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy: 3-12 mg/kg once daily, depending on the extent and duration of the induced neutropenia (refer to section 4.2 , Adults).

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.

Special populations

Elderly

Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance < 50 mL/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 50 mg to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatine Clearance (mL/min)	Percent of Recommended Dose
>50	100%
11-50	50%
Patients receiving regular 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	$\frac{\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885}{72 \times \text{serum creatine (mmol/L)}}$
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.

Method of administration

Orally administered. Fluconazole can be taken with or without food.

4.3. Contraindications

OZOLE 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 per day or higher based upon results of a multiple dose interaction study. Co-administration of other drugs known to prolong the QT interval, and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine is contraindicated in patients receiving fluconazole (refer to section 4.4 and section 4.5).

4.4. Special warnings and precautions for use

Anaphylaxis has been reported in rare instances.

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

Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of 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 (refer to section 4.8).

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of serious cutaneous reactions to many drugs. If rash which is attributable to fluconazole develops in a patient treated for a superficial fungal infection, 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 (refer to section 4.8).

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole cause 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 (refer to 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 torsades de pointes. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions (refer to section 4.8).

In rare cases, as with other azoles, anaphylaxis has been reported.

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

Fluconazole is a moderate CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of isoenzyme CYP2C19. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4 should be monitored (refer to section 4.5).

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

Reversible cases of adrenal insufficiency were reported in patients receiving fluconazole.

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

4.5. Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP 2C and to a lesser extent the CYP 3A isoforms. *In vitro* studies conducted in human hepatic microsomes, demonstrate that the extent of inhibition of CYP 3A isoforms is lowest with fluconazole, when compared with ketoconazole and itraconazole. In addition to the observed/ documented interactions mentioned below, 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.

As fluconazole is a potent inhibitor of CYP2C9, CYP2C19 and moderate inhibitor of CYP3A4, particular caution should be exercised when fluconazole is co-administered with other compounds metabolised by these isoenzymes and these 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 (refer to section 4.3).

Interactions between fluconazole and other agents

Clinically or potentially significant drug interactions observed between fluconazole and the following agents are described below.

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

Alfentanil

A study observed a reduction in clearance and distribution volume as well as prolongation of $t_{1/2}$ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

Amiodarone

Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Caution must be exercised if concomitant use of fluconazole and amiodarone is necessary, notably with high-dose fluconazole (800 mg).

Amitriptyline, nortriptyline

Fluconazole increases the effect of amitriptyline and nortriptyline. 5- nortriptyline and/or S- amitriptyline may be measured at initiation of the combination therapy and after one week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericin B

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.

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 (refer to section 4.3).

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 increases in midazolam concentrations and psychomotor effects following oral administration of midazolam 7.5 mg, but only modest increases that are not likely to be clinically significant following intravenous infusion of midazolam 0.05 mg/kg.

This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. There have been reports of sleepiness and disturbed consciousness in patients taking fluconazole for systemic mycoses and triazolam; however, in most of these cases the patients had serious underlying illnesses and/or concomitant therapies that could have contributed to the reported events, and a relationship to a fluconazole-triazolam interaction is uncertain. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored. Fluconazole increases the area under the concentration versus time curve (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.

Cisapride

There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were co-administered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illness. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Coadministration of cisapride is contraindicated in patients receiving fluconazole (refer to section 4.3).

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.

Erythromycin

Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsade de pointes) and consequently sudden heart death. This combination should be avoided.

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 twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

Halofantrine

Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4.

HMG-CoA reductase inhibitors

The risk of myopathy and rhabdomyolysis increases when fluconazole is co-administered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and 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.

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 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.

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 AUC of fluconazole, compared to fluconazole given alone. Overall the plasma concentrations of fluconazole were approximately 3.26 - 6.52 $\mu\text{mol/L}$ higher with concomitant diuretic. These

changes are attributable to a mean net reduction of approximately 20% in renal clearance of fluconazole.

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.

Losartan

Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin II-receptor antagonism that occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone

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

Non-steroidal anti-inflammatory drugs

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other non-steroidal anti-inflammatory drugs (NSAIDs) that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Olaparib

Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.

Oral contraceptives

Three kinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinylestradiol and levonorgestrel were increased 40% and 24%, respectively. In a 300 mg once weekly fluconazole study, the AUCs of ethinylestradiol and norethindrone were increased by 24% and 13%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Oral hypoglycaemic agents

The effects of fluconazole on the pharmacokinetics of the 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 coadministered, blood glucose concentrations should be monitored carefully and the dose of the sulphonylurea adjusted accordingly.

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 (refer to section 4.3).

Phenytoin

Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone

There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three-month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

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.

Rifabutin

There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

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.

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 is recommended during coadministration.

Tacrolimus

Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Theophylline

In a placebo-controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance of theophylline. Patients who are receiving high 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.

Terfenadine

Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (refer to section 4.3).

Tofacitinib

Exposure of tofacitinib is increased when tofacitinib is co-administrated 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)

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

Warfarin

A single dose of warfarin (15 mg) given to normal volunteers, following 14 days of orally administered fluconazole (200 mg) resulted in a 12% increase in the prothrombin time response (area under the prothrombin time-time curve). One 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

Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200 mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment crossover study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200 mg every eight hours either with or without fluconazole 400 mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

4.6. Fertility, pregnancy and lactation

Pregnancy

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.

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

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

There 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 -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. 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.

Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole. 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.

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.

4.7. Effects on ability to drive and use machines

Experience with fluconazole indicates that therapy is likely to produce minor or moderate adverse effects on the ability to drive or use machinery. When driving vehicles or operating machinery it should be taken into account that occasionally dizziness or seizures may occur.

4.8. Undesirable effects

Adults

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 (refer to 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:

Common ($\geq 1\%$ and $< 10\%$)	
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea
Nervous system disorders	Headache

Uncommon (≥ 0.1% to < 1%)	
Nervous system disorders	Seizures, dizziness, paraesthesia, taste perversion
Skin and subcutaneous tissue disorder	Rash
Rare (≥ 0.01% and < 0.1%)	
Blood and lymphatic system disorders	Leukopenia (including neutropenia and agranulocytosis), thrombocytopenia
Immunological system disorders	Anaphylaxis, angioedema
Metabolism and nutrition disorders	Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia
Nervous system disorders	Tremors
Skin and subcutaneous tissue disorders	Angioedema, exfoliative skin disorders including Steven Johnson Syndrome and toxic epidermal necrolysis (refer to section 4.4), alopecia

Single 150 mg dose for vaginal candidiasis

Common (≥ 1% and < 10%)	
Gastrointestinal disorders	Nausea, abdominal pain, diarrhoea, dyspepsia
Hepato-biliary disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
Nervous system disorders	Headache
Uncommon (≥ 0.1% to < 1%)	
Eye disorders	Abnormal vision
Gastrointestinal disorders	Constipation, flatulence, vomiting, loose stools, dry mouth
General disorders and administration site conditions	Thirst, fatigue, malaise, pain, rigors, asthenia, fever
Infections and infestations	Pharyngitis, herpes simplex
Metabolism and nutrition disorders	Anorexia
Musculoskeletal and connective tissue disorders	Back pain, myalgia
Nervous system disorders	Dizziness, vertigo, hyperkinesia, hypertonia, taste perversion, visual field defect
Psychiatric disorders	Insomnia, nervousness
Renal and urinary disorders	Polyuria, renal pain
Reproductive system and breast disorders	Intermenstrual bleeding, dysmenorrhoea, leukorrhoea, menorrhagia, uterine spasm, vaginal disorder, female sexual dysfunction
Skin and subcutaneous tissue disorders	Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria
Vascular disorders	Flushing, hot flushes
Rare (≥ 0.01% and < 0.1%)	
Hepato-biliary disorders	Hepatic toxicity, including rare cases of fatalities. Hepatic failure, hepatocellular necrosis, hepatitis hepatocellular damage
Cardiac disorders	Torsade de pointes, QT prolongation

Patients treated with 150 mg weekly in dermal therapeutic studies

Common (≥ 1% and < 10%)	
Gastrointestinal disorders	Abdominal pain, dyspepsia
Nervous system disorders	Headache
Skin and subcutaneous tissue disorders	Acne
Uncommon (≥ 0.1% to < 1%)	
Investigations	Elevation of transaminase > 2-3 x upper limit of normal
Nervous system disorders	Paraesthesia, somnolence
Psychiatric disorders	Insomnia
Skin and subcutaneous tissues disorders	Pruritus, urticaria, increased sweating, drug eruption (including fixed drug eruption).

Paediatrics

In clinical studies, 562 children, from birth to 17 years, received doses from 1 to 12 mg/kg per day, for up to 129 days. The majority of patients (n=522) received 2 to 8 mg/kg per 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:

Common (≥ 1% and < 10%)	
Gastrointestinal disorders	Vomiting, diarrhoea, abdominal pain
Uncommon (≥ 0.1% to < 1%)	
Cardiac disorders	Cardiomyopathy
Ear and labyrinth disorders	Deafness
Gastrointestinal disorders	Nausea, dyspepsia, ileus, stomatitis, loose stools
Hepatobiliary disorders	Hepatocellular damage, jaundice
Infections and infestations	Infection
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Headache, taste perversion
Respiratory, thoracic and mediastinal disorders	Hypoxia, respiratory disorder
Skin and subcutaneous tissue disorders	Rash (erythematous & maculo-papular), pruritus, purpura
Vascular disorders	Hypertension

Post marketing experience

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

Cardiac disorders	Torsade de pointes (refer to section 4.3 and 4.4)
Gastrointestinal disorders	Dyspepsia, vomiting
Hepatobiliary disorders	Hepatocellular necrosis
Immune system disorders	Anaphylaxis (including face oedema, angioedema and pruritus)

Investigations	QT prolongation (refer to section 4.3 and 4.4)
Metabolism and nutritional 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 reactions <https://nzphvc.otago.ac.nz/reporting/>

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 8,200 mg of fluconazole. The patient was admitted to hospital, and his condition resolved within 48 hours.

Signs and symptoms are likely to be an extension of those under 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 rates. A three-hour haemodialysis session decreases plasma level by approximately 50%.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01

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

Fluconazole, when given orally, 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 *Microsporium* 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 adrenocorticotrophic 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.

5.2. Pharmacokinetic properties

Absorption

After oral administration fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration of fluconazole. 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 (refer to 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 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)
9mos-13yrs	<u>Single oral:</u>				
	2 mg/kg	0.40	25.0	2.9	-
	8 mg/kg	0.51	19.5	9.8	-
5yrs-15yrs	<u>Multiple I.V.:</u>				
	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 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.

5.3. Preclinical safety data

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 x recommended human dose). Male rats treated with 5 mg/kg/day and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The ingredients present inside the 50 mg or 200 mg OZOLE capsules include: maize starch, sodium lauryl sulphate, colloidal anhydrous silica, and magnesium stearate.

In addition, the capsules shells contain: gelatin, patent blue (E133) and titanium dioxide (E171) for the 50 mg capsules and gelatin, patent blue (E133), erythrosine (E127) and titanium dioxide (E171) for the 200 mg capsules. The black colour in the printing ink is black iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

Ozole capsules: Blister pack, PVC/PVDC/Al foil; 28 or 30 capsules.

Not all pack size and strength maybe marketed.

6.6. Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

09 March 2006

10. DATE OF REVISION OF THE TEXT

18 September 2020

Summary table of changes

Section Changed	Summary of new information
4.6	Additional statement as per Medsafe request: <i>A study found any maternal exposure to fluconazole during pregnancy may increase the risk of spontaneous abortion and that doses higher than 150 mg during the first trimester may increase the risk of cardiac septal closure anomalies.</i>