

## ***m*-Fluconazole**

### **Fluconazole 50mg, 100mg, 150mg and 200mg Capsules**

### **Fluconazole 2mg/ml Solution for IV Infusion**

---

#### **Presentation**

---

*m*-Fluconazole 50mg capsules are size 2 green and white capsules typically weighing 180.5mg. Each capsule contains 50mg fluconazole.

*m*-Fluconazole 100mg capsules are size 1 buff coloured capsules typically weighing 310mg. Each capsule contains 100mg fluconazole.

*m*-Fluconazole 150mg capsules are size 0 yellow capsules typically weighing 445.6mg. Each capsule contains 150mg fluconazole.

*m*-Fluconazole 200mg capsules are size 0 white capsules typically weighing 562mg. Each capsule contains 200mg fluconazole.

*m*-Fluconazole 2mg/ml solution for IV infusion is a clear colourless solution containing 2mg/ml fluconazole in 0.9% saline solution. Each 25ml vial contains 50mg fluconazole, each 50ml vial contains 100mg fluconazole and each 100ml vial contains 200mg fluconazole.

---

#### **Uses**

---

##### ***Actions***

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

Fluconazole, both orally and intravenously administered, 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 medicines 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 50mg daily given up to 28 days has been shown not to affect corticosteroid levels or ACTH stimulated response in healthy female volunteers. Plasma oestradiol levels and urinary free cortisol levels were decreased with little effect on plasma testosterone levels. Interaction studies with anitypyrine indicate that single or multiple doses of fluconazole 50mg do not affect its metabolism.

##### ***Pharmacokinetics***

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

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. 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.

<b>Tissue of Fluid</b>	<b>Tissue (Fluid): Plasma Concentration*</b>
Cerebrospinal fluid <sup>†</sup>	0.5 – 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Blister skin	2

\*Relative to concurrent concentrations in plasma in subjects with normal renal function  
† Independent of degree of meningeal inflammation

The major route of excretion is renal with approximately 80% of the administered dose appearing in the urine as unchanged drug. 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 Dosage and Administration). A 3-hour haemodialysis session reduces plasma concentration by about 50%.

The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing in the treatment of all other indicated fungal infections.

## **Children**

There are differences in the pharmacokinetics of fluconazole between adults and children, with children after the neonatal period generally having a faster elimination rate and larger volume of distribution than adults. These differences result in less accumulation on multiple dosing in children, with steady state achieved faster than in adults. Neonates have reduced elimination rates relative to adults and even higher volumes of distribution in comparison to 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 <sub>max</sub> (mcg/mL)	V <sub>dss</sub> (L/kg)
9 months – 13 years	<u>Single oral:</u> 2mg/kg	0.40	25.0	2.9	-
	8mg/kg	0.51	19.5	9.8	-
5 years – 15 years	<u>Multiple IV:</u> 2mg/kg	0.49	17.4	5.5	0.722
	4mg/kg	0.59	15.2	11.4	0.729
	8mg/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.

### **Indications**

Fluconazole is indicated for the treatment of the following conditions:

1. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary and cutaneous). Normal hosts, and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 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. *m*-Fluconazole 50mg and 150mg capsules are also indicated for the treatment of dermatomycoses including tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor and candidiasis.

*m*-Fluconazole solution for IV infusion is indicated for the same conditions in patients, but should be used only when oral administration is not possible.

---

### **Dosage and Administration**

---

The daily dose of fluconazole should be based on the nature and severity of the fungal infection. 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**

1. **(a) 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 6-8 weeks for cryptococcal meningitis.  
**(b) 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 200mg.
2. **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.
3. **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.

For other candidal infections of mucosa (except vaginal candidiasis, see below) e.g. oesophagitis, candiduria, mucocutaneous candidiasis etc., the usual effective dose is 50mg daily, given for 14-30 days.

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

4. **Vaginal candidiasis:** Fluconazole 150mg should be administered as a single oral dose. Median time to onset of symptom relief following a 150mg 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.
5. **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.
6. **Dermatomycoses:** The usual dosage is 50mg once daily or 150mg once weekly for 2 to 4 weeks. Tinea pedis may require treatment for up to 6 weeks.

## **Children**

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 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 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 daily, depending on the extent and duration of the induced neutropenia (see adult dosing).

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

### **Children 4 weeks of age and younger**

Neonates excrete fluconazole slowly. In the first 2 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.

### **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.

### **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:

<b>Creatinine clearance (mL/min)</b>	<b>Percent of Recommended Dose</b>
> 50	100%
11 – 50	50%
Patients receiving regular dialysis	One dose after every dialysis 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/min:

Males:  $\text{Weight (kg)} \times (140 - \text{age}) \times 0.0885$

$\frac{\quad}{72 \times \text{serum creatinine (mmol/L)}}$

Females: 0.85 x above value

### **Intravenous Administration**

The dose recommendations for oral and intravenous *m*-Fluconazole are identical.

Fluconazole is normally administered orally. If oral administration is not possible, it may be administered by IV infusion at a rate not exceeding 200mg/hour, given as a constant infusion. Fluconazole infusion has been used safely for up to 14 days of IV therapy. Since oral absorption is rapid and almost complete, there is no need to change the daily dosage on transferring from the IV to the oral route or vice versa.

The daily dose of fluconazole should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical parameters or laboratory

tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis often require maintenance therapy to prevent relapse.

If *m*-Fluconazole infusion is administered to patients requiring sodium or fluid restriction, consideration should be given to the salt content of the infusion fluid (7.5 mmol/50mL) and the total volume of fluid administered.

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

*m*-Fluconazole intravenous infusion is compatible with the following:

- a. Ringer's solution
- b. Normal saline
- c. Dextrose 20%
- d. Hartmann's solution
- e. Potassium chloride in dextrose
- f. Sodium bicarbonate 4.2%

*m*-Fluconazole infusion 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 medicine prior to infusion is not recommended.

Parenteral medicine products should be inspected visually for particulate matter and discoloration 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.

---

## Contraindications

---

*m*-Fluconazole should not be used in patients with known sensitivity to fluconazole, to relatedazole compounds or to any of its excipients.

Concomitant administration of fluconazole with cisapride is contraindicated (see Interactions).

---

## Warnings and Precautions

---

Anaphylaxis has been reported in rare instances.

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

Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see Adverse Effects).

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 medications. 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 or systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop (see Adverse Effects).

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions (see Adverse Effects).

### ***Use in Pregnancy and Lactation***

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 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. 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.

Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

### **Driving or Use of Machinery**

Experience with fluconazole indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

---

## **Adverse 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.

#### **1. 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 Warnings and Precautions. There have been rare cases of serious hepatic reactions during treatment with fluconazole (see Warnings and Precautions). 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:

<b>Common (≥1% and &lt;10%)</b>	
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea
Nervous system disorders	Headache
Skin and subcutaneous tissue disorders	Rash
<b>Rare (≥0.01% and &lt;0.1%)</b>	
Blood and lymphatic system disorders	Leukopenia (including neutropenia and agranulocytosis), thrombocytopenia
Immunological system disorders	Anaphylaxis
Metabolism and nutrition disorders	Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia
Nervous system disorders	Seizures
Skin and subcutaneous tissue disorders	Angioedema, exfoliative skin disorders including Stevens–Johnson Syndrome and toxic epidermal necrolysis (see Warnings and Precautions), alopecia

## 2. Single 150 mg dose for vaginal candidiasis

<b>Common (≥1% and &lt;10%)</b>	
Gastrointestinal disorders	Nausea, abdominal pain, diarrhoea, dyspepsia

Nervous system disorders	Headache
<b>Uncommon (≥0.1% and &lt;1%)</b>	
Eye disorders	Abnormal vision
Gastrointestinal disorders	Constipation, flatulence, vomiting, loose stools, dry mouth
General disorders and administration site conditions	Thirst, fatigue, malaise, pain, rigors
Infections and infestations	Pharyngitis, herpes simplex
Metabolism and nutrition disorders	Anorexia
Musculoskeletal and connective tissue disorders	Back pain
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 tissues disorders	Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria
Vascular disorders	Flushing, hot flushes

### 3. Patients treated with 150 mg weekly in dermal therapeutic studies

<b>Common (≥1% and &lt;10%)</b>	
Gastrointestinal disorders	Abdominal pain, dyspepsia
Nervous system disorders	Headache
Skin and subcutaneous tissue disorders	Acne
<b>Uncommon (≥0.1% and &lt;1%)</b>	
Investigations	Elevation of transaminase >2-3 x upper limit of normal
Nervous system disorders	Paraesthesia, somnolence
Psychiatric disorders	Insomnia
Skin and subcutaneous tissue disorders	Pruritus, urticaria

## **Children**

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:

<b>Common (≥1% and &lt;10%)</b>	
Gastrointestinal disorders	Vomiting, diarrhoea, abdominal pain
<b>Uncommon (≥0.1% and &lt;1%)</b>	
Cardiac disorders	Cardiomyopathy
Ear and labyrinth disorders	Deafness
Gastrointestinal disorders	Nausea, dyspepsia, ileus, stomatitis, loose stools
Hepatobiliary disorders	Hepatocellular damage, jaundice
Infection 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 and 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 (see Warnings and Precautions)

**Gastrointestinal disorders:** Dyspepsia, vomiting

**Hepatobiliary disorders:** Hepatocellular necrosis

**Immune system disorders:** Anaphylaxis (including face oedema, angioedema and pruritus)

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

**Metabolism and nutrition disorders:** Hypercholesterolaemia, hypertriglyceridemia and hypokalaemia

**Nervous system disorders:** Dizziness

---

## 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. Co-administration of fluconazole with some other drugs metabolised primarily by these P450 isoforms may result in altered plasma concentrations of these drugs that could change therapeutic effects and/or adverse event profile.

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.

**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.

**Cisapride:** There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. 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 (see Contraindications).

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

**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 micromol/L higher with concomitant diuretic. These changes are attributable to a mean net reduction of approximately 20% in renal clearance of fluconazole.

**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 ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. In a 300 mg once weekly fluconazole study, the AUCs of ethinyl estradiol 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.

**Phenytoin:** Concomitant administration of oral fluconazole (200 mg) with phenytoin at steady state resulted in an average increase of 75% of phenytoin AUC values in normal volunteers. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended.

**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 coadministered. 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.

**Tacrolimus:** There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were coadministered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

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

**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 otherazole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melena) have been reported in association with increases in prothrombin time in patients

receiving fluconazole concurrently with warfarin. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended.

**Zidovudine:** 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.

---

## Overdosage

---

There have been case reports of overdosage with fluconazole and in one case, a 42 year old patient infected with HIV developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8.2g of fluconazole. The patient was admitted to hospital, and his condition resolved within 48 hours.

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

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%.

In mice and rats receiving very high doses of fluconazole, clinical effects, in both species, included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex and cyanosis; death was sometimes preceded by clonic convulsions.

---

## Pharmaceutical Precautions

---

Store below 25°C. Protect from heat, light and moisture.

---

## Medicine Classification

---

50mg, 100mg, 200mg capsules and 2mg/ml infusion solution: Prescription Medicine

150mg capsule (single dose) for the treatment of vaginal candidiasis: Pharmacist Only Medicine

---

## Package Quantities

---

2mg/ml IV infusion solution: Packs of 1 vial containing 25ml, 50ml or 100ml.

50mg capsules: Packs of 28 capsules

100mg capsules: Packs of 28 capsules

150mg capsules: Packs of 1 capsule

200mg capsules: Packs of 28 capsules

*(Not all strengths and pack sizes may be marketed)*

---

**Further Information**

---

Nil

---

**Name and Address**

---

Multichem NZ Ltd.  
8 Apollo Drive  
Mairangi Bay  
Private Bag 93-527  
Takapuna  
Auckland

Tel: (09) 488-0330  
Fax: (09) 478-3841

---

**Date of Preparation**

---

9 January 2008