**AUSTRALIAN PRODUCT INFORMATION**
**FLUCONAZOLE APOTEX**
**(Fluconazole)**

## 1 NAME OF THE MEDICINE

Fluconazole.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluconazole Apotex contains fluconazole 200 mg.

Excipient with known effects: lactose monohydrate.

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

## 3 PHARMACEUTICAL FORM

Capsule.

Purple/ white hard gelatin, self-locked capsules of size '0' containing white to off white powder.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Fluconazole capsules given orally are indicated for the following conditions:

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

  NOTE: Data suggest that the clinical efficacy of fluconazole is lower than that of amphotericin B in the treatment of the acute phase of cryptococcal meningitis.

- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with AIDS.

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

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

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

  NOTE: It remains to be shown that fluconazole is as effective as amphotericin B in the treatment of serious and life-threatening *Candida* infections. Until such data are available, amphotericin B remains the drug of choice.

- Vaginal candidiasis, when topical therapy has failed.

- Treatment of extensive tinea corporis, extensive tinea cruris and extensive tinea pedis infections in immunocompetent patients in whom topical therapy is not a practical treatment option. Usually, topical therapy should be attempted first because oral therapy has a less favourable ratio of benefits to risks.

## 4.2 DOSE AND METHOD OF ADMINISTRATION

**Adults**
*For cryptococcal meningitis in patients who are unable to take or tolerate amphotericin B:* The usual dose is 400 mg on the first day followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgement of the patient's response to therapy. Patients not responding to treatment for up to 60 days would appear unlikely to respond to fluconazole.
Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but should continue 10-12 weeks after cerebrospinal fluid becomes culture negative. Negative serology does not necessarily indicate eradication of the disease; a proportion of such patients relapse in due course.

*Prevention of relapse of cryptococcal meningitis in AIDS patients:* After the patient receives a full course of primary therapy, fluconazole may be administered at a daily dose of 100-200 mg.

*Oropharyngeal candidiasis:* the recommended dose is 100 mg on the first day followed by 50 mg once daily. For the treatment of oesophageal candidiasis the recommended dose is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of candidiasis usually resolves within several days, but treatment should be continued for at least two to three weeks especially in patients with severely compromised immune function. Patients with severe oesophageal candidiasis may need treatment to be continued for two weeks following resolution of symptoms. Approximately half of the clinically cured patients remain colonised.

*Secondary prophylaxis against oropharyngeal candidiasis in patients with HIV infections:* The recommended dose is 150 mg as a single dose once weekly.

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

*Vaginal candidiasis when topical therapy has failed:* Fluconazole 150 mg should be administered as a single oral dose
In those patients who responded to treatment, the median time to onset of symptom relief was one deay (range: 0.04-9 days) and to complete symptom relief was two days (range: 0.5-20 days).

*For extensive tinea infections (tinea corporis, tinea cruris), or severe tinea pedis in immunocompetent patients in whom topical therapy is not practical;* The recommended dosage is 150 mg once weekly for 4 weeks.

**Children**
Fluconazole capsules are not suitable for children weighing under 35 kg.

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: The recommended dosage is 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.

Systemic candidiasis and cryptococcal infection: The recommended dosage is 6 to 12 mg/kg daily, depending on the severity of the disease.
For children with impaired renal function the daily dose should be reduced in accordance with the guidelines given for adults.

**Elderly**
Dose should be adjusted for elderly patients with renal impairment.

**Renal Impairment**
Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single-dose therapy are necessary. In multiple-dose treatment of patients with renal impairment, normal doses should be given on days 1 and 2 of treatment and thereafter the dosage intervals or the daily dose should be modified in accordance with creatinine clearances as follows:

| **Creatinine Clearance (mL/min)** | **Dosage Intervals/Daily Dose** |
|---|---|
| >50 | 24 hours (normal dosage regimen) |
| 21-50 | 48 hours or half normal daily dose |
| 11-20 | 96 hours or one-quarter normal daily dose |

Patients receiving regular dialysis: One recommended dose after every dialysis session. These are suggested dose adjustments based on pharmacokinetics following administration of single doses. Further adjustment may be needed depending on clinical condition.

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of patient) should be used to estimate the creatinine clearance in mL/minute.

| | |
|---|---|
| Males: | Weight (kg) X (140-age) X 0.0885 |
| | 72 X serum creatinine (mmol/L) |

| |
|---|
| Females: 0.85 X above value |

**4.3 CONTRAINDICATIONS**
FLUCONAZOLE APOTEX (fluconazole) capsules are contraindicated in the following conditions:

- Patients with known sensitivity to fluconazole; to related azole compounds; or to any of its excipients.
- Concomitant administration with cisapride.

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

**General**
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 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.

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.

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.

**Use in the elderly**
No data available.

**Paediatric use**
No data available.

**Effects on laboratory tests**
No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP 2C and to a lesser extent the CYP 3A isoforms. Co-administration of fluconazole with some other drugs metabolized primarily by these P450 isoforms may result in altered plasma concentrations of these drugs that change therapeutic effects and or adverse event profiles.
Clinically or potential significant drug interactions have been observed between fluconazole and the following agents: short acting benzodiazepines, cisapride, coumarin-type anticoagulants, cyclosporin, hydrochlorothiazide, oral hypoglycaemics, phenytoin, rifampicin, rifabutin, tacrolimus and theophylline. These are described in greater detail below.

***Effect 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 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***

Concomitant use of the following agents with fluconazole is contraindicated:
*Cisapride:* Fluconazole 200 mg daily increased the AUC and $C_{max}$ of cisapride (20 mg four times daily) both after a single dose (AUC increased 101% and $C_{max}$ increased 91%) and multiple doses (AUC increased 192% and $C_{max}$ increased 154%). A significant prolongation in QTc interval was recorded. Cardiac events including torsades 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.

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

*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. Plasma cyclosporin levels should be monitored in all patients receiving concomitant fluconazole.

*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 co-administered, 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.

*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 other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria and

melena) have been reported, in asssociation 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.

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 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 either 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 of 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 µg and norethindrone 0.5 mg. AUC of ethinyl estradiol was increases 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, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycinon on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effect of fluconazole on the pharmacokinetics of azithromycin. The estimated ratio of the mean AUC of fluconazole coadministered with azithromycin to fluconazole administered alone was 101%. The estimated ratio of the mean AUC of azithromycin coadministered with fluconazole to azithromycin alone was 107 %. The estimated ratio of the mean $C_{max}$ of fluconazole coadministered with azithromycin to fluconazole administered alone was 104%. The estimated ratio of the mean $C_{max}$ of azithromycin coadministered with fluconazole to azithromycin administered alone was 82%.

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]<br>Rifampicin[2] | Benzodiazapines (short-acting)[5]<br>Cyclosporin[4]<br>Oral hypoglycaemics[3]<br>Phenytoin[4]<br>Rifabutin[5]<br>Tacrolimus[1]<br>Theophylline[5]<br>Warfarin[6]<br>Zidovudine[5] | Antacids<br>Azithromycin<br>Cimetidine<br>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

**Effects on fertility**
Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 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 stillborn pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

**Use in pregnancy**
Category D. 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 coccidiomycosis. 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.

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

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## 4.8 ADVERSE EFFECTS (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. There have been rare cases of serious hepatic reactions during treatment with fluconazole. 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 include the following:

*Blood and lymphatic system disorders:*

Rare: leukopenia (including neutropenia and agranulocytosis), thrombocytopenia
*Gastrointestinal:*
Common: nausea, vomiting, abdominal pain, diarrhoea.
*Immunological system disorders:*
Rare: anaphylaxis.
*Metabolism and nutritional disorders:*
Rare: hypercholesterolaemia, hypertriglyceridaemia, hypocalemia
*Nervous System disorders:*
Common: headache.
Rare: seizures.
*Skin and subcutaneous disorders:*
Common: rash.
Rare: angioedema, exfoliative skin disorders including Steven Johnson Syndrome and toxic epidermal necrolysis, alopecia.

*Single 150 mg dose for vaginal candidiasis*
*Eye disorders:*
Uncommon: abdominal pain
*Gastrointestinal disorders:*
Common: nausea, dyspepsia, abdominal pain, diarrhoea.
Uncommon: constipation, flatulence, vomiting, loose stools, dry mouth.
*General disorders and administration site conditions:*
Uncommon: thirst, fatigue,malaise,pain,rigors
*Infections and infestations:*
Uncommon: pharyngitis, herpes simplex
*Metabolism and nutritional disorders:*
Uncommon: anorexia
*Musculoskeletal and connective tissue disorders:*
Uncommon: back pain
*Nervous system disorders:*
Common: headache
Uncommon: Dizziness, vertigo, hyperkinesia, hypertonia, taste perversion, visual fieled 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 tissue disorders:*
Uncommon: pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria.
*Vascular disorders:*
Uncommon: flushing, hot flushes.

3. *Patients treated with 150 mg weekly in dermal therapeutic studies:*
*Gastrointestinal disorders:*
Common: dyspepsia, abdominal pain.
*Investigation:*

Uncommon: elevation of transaminase > 2.3 x upper limit of normal.
*Nervous System disorders:*
Common: headache.
Uncommon: paraesthesia, somnolence.
*Psychiatric disorders:*
Uncommon: insomnia,
*Skin and subcutaneous tissue disorders:*
Uncommon: 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:
*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.
*Metabolic and nutritional disorders:*
Uncommon: anorexia.
*Nervous system disorders:*
Uncommon: headache, taste perversion.
*Respiratory, thoracic and mediastinal disorders:*
Uncommon: hypoxia & respiratory disorder
*Skin and subcutaneous disorders:*
Uncommon: rash (erythematous & maculo-papular) pruritus, purpura.
*Vascular disorders:*
Uncommon: hypertension.

Post-Marketing Experience:
In addition the following adverse events have occurred during post-marketing:
*Cardiac disorders:* QT prolongation, torsade de pointes.
*Gastrointestinal disorders:* dyspepsia, vomiting
*Hepatobiliary disorders:* hepatocellular necrosis
*Immune system disorders:* anaphylaxis (including face adema, angiodema and pruritus)
*Metabolic and nutritional disorders:* hypercholesterolemia, hypertriglyceridemia and hypokalemia.
*Nervous System disorders:* dizziness

**Reporting suspected adverse effects**
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

### 4.9 Overdose

There have been reports of overdosage with fluconazole, and in one case, a 42-year-old patient infected with 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.
In the event of overdosage, symptomatic treatment (with supportive measures if necessary) should be undertaken. **Contact the Poisons Information Centre on 131126 (Australia) for advice on management.**

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.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**
Fluconazole is a member of the bis-triazole class of antifungal agents. Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14 alpha-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole. Fluconazole 50 mg daily given up to 28 days has been shown not to affect corticosteroid levels or 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 antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

**Clinical trials**
No data available.

### 5.2 PHARMACOKINETIC PROPERTIES

***Absorption***
The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. In fasted normal volunteers, peak plasma concentrations (Cmax) of 3.67 /mL occurred in 4.02 hours (time to maximum serum concentration) after an oral dose of 200 mg fluconazole (FLUCONAZOLE APOTEX) capsule.

***Distribution***
Plasma concentrations are proportional to dose and steady-state levels are reached within 5-10 days with oral doses of 50-400 mg once daily. Steady-state levels are approximately 2.5 times the levels achieved with single doses. Administration of loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

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

| **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

***Metabolism***
Following 100 mg dose of fluconazole a terminal plasma elimination half-life was reported to be approximately 30 hours (range 20 to 50 hours) in adults.

***Excretion***
The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for all other indications.

***Special populations***
***Renal Impairment:***
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 **DOSE AND METHOD OF ADMINISTRATION**). A 3-hour haemodialysis session reduces plasma concentration by about 50%.

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

children. During the first 2 weeks after birth, the clearance of fluconazole increases (and the half-life is decreased) as renal function develops. The half-life obtained in infants was consistent with that found in older children, although the volume of distribution was higher. During the first year of life, the pharmacokinetics of fluconazole 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)** | **Vdss (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 years – 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 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.

**Microbiology**
Fluconazole administered orally or intravenously was active in a variety of animal models of fungal infections using standard laboratory strains of fungi.
Fluconazole exhibits *in vitro* activity against *Cryptococcus neoformans* and *Candida* spp. Activity has been demonstrated *in vivo* in normal and immunocompromised animals against infections with *Candida* spp, including systemic candidiasis and in normal animals with *C. neoformans*, including intracranial infections. One case of cross-resistance of *Candida* to fluconazole in a patient (non-HIV) previously treated with ketoconazole has been reported. The efficacy of fluconazole *in vivo* is greater than would be apparent from *in vitro* testing against the above-mentioned fungi.
Concurrent administration of fluconazole and amphotericin B in infected normal and immunocompromised mice showed antagonism of the two drugs in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**
Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *Salmonella typhimurium* and in the mouse lymphoma system. Cytogenetic studies *in vivo* and *in vitro* showed no evidence of chromosomal mutations.

**Carcinogenicity**
Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2-7 x recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS
Lactose monohydrate, maize starch, colloidal anhydrous silica, magnesium stearate and sodium lauryl sulfate.

*Capsule shell composition*:
Patent blue V, titanium dioxide, gelatin, erythrosine, purified water.

### 6.2 INCOMPATIBILITIES
See Section 4.5 Interactions with other medicines and other forms of interactions.

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

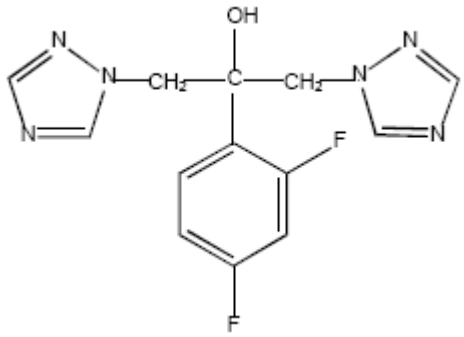
### 6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C

### 6.5 NATURE AND CONTENTS OF CONTAINER
Blister (PVC/PVDC/Al) containing 28 capsules per pack.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7 PHYSIOCHEMICAL PROPERTIES

**Chemical structure**




**Molecular Formula**: $C_{13}H_{12}F_2N_6O$
**Molecular weight:** 306.3.
**CAS Number:** 86386-73-4

Fluconazole is a member of the bis-triazole class of antifungal agents. It is chemically designated as 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol.

Fluconazole is a white crystalline powder, slightly soluble in water, freely soluble in methanol.

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

## 8. SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Tel: (02) 8877 8333
Web: www1.apotex.com/au

## 9. DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 07/12/2017

## 10 DATE OF REVISION

Date of the most recent TGA approved changes to the approved PI: 02/07/2018

**Summary table of changes**

| Section Changed | Summary of new information |
|---|---|
| 3. | Pharmaceutical Form |
| 6.1 | Updated medicine ingredient names and minor correction |