

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 100mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluconazole 100mg.

Excipients: Lactose monohydrate 104.78mg, for a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Fluconazole 100mg capsules are light blue and white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly. Fluconazole 100mg capsules are indicated for the treatment of the following conditions:

1. Genital candidiasis. Vaginal candidiasis, acute or recurrent, Candidal balanitis. The treatment of partners who present with symptomatic genital candidiasis should be considered.
2. 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.
3. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections. Fluconazole 100mg capsules are not indicated for nail infections.
4. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium and pulmonary and urinary tracts. Candidal infections in patients with malignancy, in intensive care units or those receiving cytotoxic or immunosuppressive therapy may be treated.
5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or

other causes of immunosuppression may be treated. Fluconazole 100mg capsules can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

6. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant patients.

4.2 Posology and method of administration

Fluconazole may be administered either orally or by intravenous infusion at a rate of approximately 5-10ml/min, the route being dependent on the clinical state of the patient. On transferring from the intravenous route to the oral route or vice versa, there is no need to change the daily dose. The daily dose 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 usually require maintenance therapy to prevent relapse.

Use in Adults

1. Candidal vaginitis or balanitis – 150mg single oral dose.

2. Mucosal Candidiasis.

Oropharyngeal candidiasis – the usual dose is 50mg once daily for 7 – 14 days. Treatment should not normally exceed 14 days except in severely immunocompromised patients.

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 genital candidiasis (see above), e.g. oesophagitis, non-invasive bronchopulmonary infections, 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.

3. For tinea pedis, corporis, cruris, versicolor and dermal Candida infections the recommended dosage is 50mg once daily. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks. Duration of treatment should not exceed 6 weeks.

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

5a For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 400mg on the first day followed by 200mg – 400mg once daily. Duration of

treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6 – 8 weeks for cryptococcal meningitis.

5b For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a daily dose of 100 – 200mg.

6. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 50 to 400mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection, e.g. patients who are anticipated to have profound or prolonged neutropenia such as during bone marrow transplantation, the recommended dose is 400mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia, and continued for 7 days after the neutrophil count rises above 1000 cells per mm³.

Use in 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 daily dose each day.

For children with impaired renal function, see dosing in “Use in patients with impaired renal function”.

Children over four weeks of age: The recommended dose of fluconazole for mucosal candidiasis is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly. For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6 – 12mg/kg daily, depending on the severity of the disease.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 – 12mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing). A maximum dosage of 400mg daily should not be exceeded in children.

Despite extensive data supporting the use of fluconazole in children there are limited data available on the use of fluconazole for genital candidiasis in children below 16 years. Use at present is not recommended unless antifungal treatment is imperative and no suitable alternative agent exists.

Children four 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.

A maximum dosage of 12mg/kg every 72 hours should not be exceeded in children in the first two weeks of life. For children between 3 and 4 weeks of life, 12mg/kg every 48 hours should not be exceeded. To facilitate accurate measurement of doses less than 10mg, fluconazole should only be administered to children in hospital using the 50mg/5ml suspension orally or the intravenous infusion, depending on the clinical condition of the child.

Use in the elderly

The normal dose should be used if there is no evidence of renal impairment. In patients with renal impairment (creatinine clearance less than 50ml/min) the dosage schedule should be adjusted as described below.

Use in patients with impaired renal function

Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required. In patients (including children) with impaired renal function who will receive multiple doses of fluconazole, the normal recommended dose (according to indication) should be given on day 1, followed by a daily dose based on the following table:

Creatinine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no dialysis) (11-50)	50%
Regular dialysis	100% after each dialysis

Fluconazole capsules should be swallowed whole.

4.3 Contraindications

Fluconazole 100 mg capsules should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any other ingredient in the formulation.

Coadministration 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, pimozone and quinidine are contraindicated in patients receiving fluconazole (see sections 4.4 Special Warnings and Precautions for Use and 4.5 Interaction with other medicinal products and Other Forms of Interaction).

4.4 Special warnings and precautions for use

Fluconazole should be administered with caution to patients with liver dysfunction (See also 4.2).

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 of fluconazole, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of fluconazole therapy.

Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or 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 severe cutaneous reactions to many drugs. If a rash develops in a patient treated for a superficial fungal infection, which is considered attributable to fluconazole, further therapy with this agent 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.

The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and Other Forms of Interaction).

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

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.

Fluconazole should be administered with caution to patients with renal dysfunction (see also section 4.2).

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolised through CYP2C9 and CYP3A4, should be monitored (see section 4.5 Interaction with other Medicinal products and Other Forms of Interaction).

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

4.5 Interaction with other medicinal products and other forms of interaction

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 co-administered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (See section 4.3).

Concomitant use of the following other medicinal products is contraindicated:

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, interactions studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly.

The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3 Contraindications). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. 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 QT interval. Because of the potential seriousness of such an interaction, co-administration of cisapride is contra-indicated in patients receiving fluconazole. (See “Contra-indications”.)

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and astemizole is contraindicated.

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.

Concomitant use of the following other medicinal products cannot be recommended:

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

Concomitant use of the following other medicinal products lead to precautions and dose adjustments:

The effect of other medicinal products on fluconazole

Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin an increase in the fluconazole dose should be considered.

Hydrochlorothiazide: In a kinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.

The effect of fluconazole on other medicinal products

Anticoagulants: In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria and melena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (Short Acting): Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. 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 AUC of triazolam (single dose) by approximately 50%, C_{max} by 20-32% and increases t_{1/2} by 25-50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

Sulphonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind. Blood glucose levels must therefore be monitored and the dose of sulphonylurea adjusted accordingly:-

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

Oral contraceptives: Two pharmacokinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50mg fluconazole study, while at 200mg daily the AUCs of ethinyloestradiol and levonorgestrel were increased 40% and 24% respectively. Thus multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

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.

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200mg for 14 days resulted in an 18% decrease in the mean plasma clearance of theophylline. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole and the therapy modified appropriately if signs of toxicity develop.

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.

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 *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two drugs in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Azithromycin: An open-label, randomized, 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.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Calcium Channel Blockers: Certain dihydropyridine calcium channel antagonists (nifedipine, isradipine, amlodipine and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking into increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomized 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 coadministered 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 creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E3174) which is responsible for most of the angiotensin II-receptor antagonism which 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: The C_{max} and AUC of flurbiprofen was increased by 23% and 81 %, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer (S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other 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.

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.

Saquinavir: Fluconazole increases the AUC of saquinavir with approximately 50%, C_{max} with approximately 55% and decreases clearance of saquinavir with approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

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, 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.

Zidovudine: Fluconazole increases C_{max} and AUC of zidovudine by 85% and 75%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.

Interaction studies have shown that when oral fluconazole is coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to an increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

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.

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.

Bosentan: Concomitant administration of fluconazole and bosentan increased the plasma concentration of bosentan; hence concomitant use should be avoided.

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.

Parecoxib: Increase in plasma concentration of parecoxib has been reported with concomitant fluconazole use and it is recommended that the dose of parecoxib be reduced, when these two drugs are given concurrently.

Valdecoxib: Increase in plasma concentration of valdecoxib has been reported with concomitant fluconazole use and it is recommended that the initial dose of valdecoxib be reduced, when these two drugs are given concurrently.

Endogenous steroid: Fluconazole 50mg daily does not affect endogenous steroid levels in females: 200mg – 400mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but that such interactions may occur.

4.6 Pregnancy and lactation

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dosage in the first trimester, show no undesired effects in the foetus.

There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear.

Animal studies show teratogenic effects (see section 5.3).

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus.

Use during lactation:

Fluconazole is 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

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

4.8 Undesirable effects

Fluconazole is generally well tolerated.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities (see section 4.4 Special Warnings and Special Precautions for Use)

have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

The following undesirable effects have been observed and reported during treatment with fluconazole with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$) and very rare ($> 1/10000$), not known (cannot be estimated from the available data).

<u>System Organ Class</u>	<u>Frequency</u>	<u>Undesirable effects</u>
<u>Blood and the lymphatic system disorders</u>	<u>Rare</u>	<u>Agranulocytosis, leukopenia, neutropenia, thrombocytopenia</u>
<u>Immune system disorders</u>	<u>Rare</u>	<u>Anaphylaxis</u>
<u>Metabolism and nutrition disorders</u>	<u>Uncommon</u>	<u>Hypokalaemia</u>
	<u>Rare</u>	<u>Hypertriglyceridaemia, hypercholesterolaemia</u>
<u>Psychiatric disorders</u>	<u>Uncommon</u>	<u>Insomnia, somnolence</u>
<u>Nervous system disorders</u>	<u>Rare</u>	<u>Tremor</u>
	<u>Common</u>	<u>Headache</u>
	<u>Uncommon</u>	<u>Seizures, dizziness, paraesthesia, taste perversion</u>
<u>Ear and labyrinth disorders</u>	<u>Uncommon</u>	<u>Vertigo</u>
<u>Cardiac disorders</u>	<u>Rare</u>	<u>Torsade de pointes, QT prolongation</u>
<u>Gastrointestinal disorders</u>	<u>Common</u>	<u>Abdominal pain, diarrhoea, nausea, vomiting</u>
	<u>Uncommon</u>	<u>Dyspepsia, flatulence, dry mouth</u>
<u>Hepato-biliary disorders</u>	<u>Common</u>	<u>Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased</u>

	<u>Uncommon</u>	<u>Cholestasis, jaundice, bilirubin increased</u>
	<u>Rare</u>	<u>Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage</u>
<u>Skin and subcutaneous tissue disorders</u>	<u>Common</u>	<u>Rash</u>
	<u>Uncommon</u>	<u>Pruritus, urticaria, increased sweating, drug eruption</u>
	<u>Rare</u>	<u>Toxic epidermal necrolysis</u> ^a <u>Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia</u>
<u>Musculoskeletal, connective tissue bone disorders</u>	<u>Uncommon</u>	<u>Myalgia</u>
<u>General disorders and administration site conditions</u>	<u>Uncommon</u>	<u>Fatigue, malaise, asthenia, fever</u>

Paediatric Population

The pattern and incidence of side effects and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.

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 8200mg of fluconazole, unverified by his physician. The patient was admitted to the hospital and his condition resolved within 48 hours.

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

As 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%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC CODE: J02AC01

Fluconazole, a member of the triazole class of antifungal agents, is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol.

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbitone sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (iv) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

Both orally and intravenously administered fluconazole was 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 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.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to fluconazole (e.g. *Candida krusei*). Such cases may require alternative antifungal therapy.

Fluconazole is highly specific for fungal cytochrome P-450 dependant enzymes. Fluconazole 50mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200-400mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50mg do not affect its metabolism.

5.2 Pharmacokinetic properties

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 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 achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentrations was still 5.8 microgram/g.

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 long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis and once daily dosing for other indications.

A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a capsule or in an oral suspension by rinsing and retaining in mouth for 2 minutes and swallowing. The maximum concentration of fluconazole in saliva after the suspension was observed 5 minutes after ingestion, and was 182 times higher than the maximum saliva concentration after the capsule which occurred 4 hours after ingestion. After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

Pharmacokinetics in Children

In children, the following pharmacokinetic data have been reported:

Age Studied	Dose (mg/kg)	Half-life (hours)	AUC (microgram.h/ml)
11 days – 11 months	Single-IV 3mg/kg	23	110.1
9 months – 13 years	Single – Oral 2mg/kg	25.0	94.7
9 months – 13 years	Single – Oral 8mg/kg	19.5	362.5
5 years – 15 years	Multiple IV 2mg/kg	17.4*	67.4
5 years – 15 years	Multiple IV 4mg/kg	15.2*	139.1
5 years – 15 years	Multiple IV 8mg/kg	17.6*	196.7

Mean Age 7 years	Multiple Oral 3mg/kg	15.5	41.6
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* Denotes final day

5.3 Preclinical safety data

Reproductive Toxicity: Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60 x the recommended human dose) to 320mg/kg embryoletality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

Carcinogenesis: Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10mg/kg/day. Male rats treated with 5 and 10mg/kg/day had an increased incidence of hepatocellular adenomas.

Mutagenesis: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S.typhimurium* and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000ug/ml) showed no evidence of chromosomal mutations.

Impairment of fertility: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize Starch

Colloidal Anhydrous Silica

Magnesium Stearate

Sodium Lauril sulfate

In addition, capsule shells contain:

Titanium, dioxide (E171)

Gelatin

Patent blue V (E131)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C

Store in the original package.

6.5 Nature and contents of container

Fluconazole capsules will be supplied in aluminium/PVC laminate blister packs.

Packs of 1, 7, 14, 28 and 56 capsules.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited

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12-16 Addiscombe Road

Croydon
Surrey
CR0 0XT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0137

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08/01/2009

10 DATE OF REVISION OF THE TEXT

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11 DOSIMETRY (IF APPLICABLE)

**12 INSTRUCTIONS FOR PREPARATION OF
RADIOPHARMACEUTICALS (IF APPLICABLE)**