



**FLUCONAZOLE TABLETS USP  
50MG/100MG/150MG/200MG  
TAJ PHARMA**

**1. NAME OF THE MEDICINAL  
PRODUCT**

Fluconazole Tablets USP 50mg Taj Pharma  
Fluconazole Tablets USP 100mg Taj Pharma  
Fluconazole Tablets USP 150mg Taj Pharma  
Fluconazole Tablets USP 200mg Taj Pharma

**2. QUALITATIVE AND  
QUANTITATIVE COMPOSITION**

a) Each tablet contains:

Fluconazole USP	50mg
Excipients	q.s.

b) Each tablet contains:

Fluconazole USP	100mg
Excipients	q.s.

c) Each tablet contains:

Fluconazole USP	150mg
Excipients	q.s.

d) Each tablet contains:

Fluconazole USP	200mg
Excipients	q.s.

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Tablet.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Fluconazole Tablets  
50mg/100mg/150mg/200mg is indicated for the treatment of the following conditions:-

Vaginal candidiasis, acute or recurrent; or candidal balanitis associated with vaginal candidiasis.

**4.2 Posology and method of administration**  
**Posology**

*In Adults aged 16-60 years:* Vaginal candidiasis or candidal balanitis – 150mg single oral dose.

*Paediatric population*

Not recommended in children aged under 16 years.

*Elderly*

Not recommended in patients aged over 60 years.

*Renal impairment*

Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required.

**Method of administration**

For oral use.

**4.3 Contraindications**

Fluconazole should not be used in patients with known hypersensitivity to fluconazole, to related azole compounds or to any of the excipients listed in section 6.1.

Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Co-administration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine, and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

**4.4 Special warnings and precautions for use**

### Hepatobiliary system

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

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

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

### Dermatological reactions

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.

### Terfenadine

The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

### Hypersensitivity

In rare cases anaphylaxis has been reported (see section 4.3).

### Cardiovascular system

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. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

### Renal System

Use with caution in patients with renal dysfunction ( see section 4.2)..

### Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be, applicable to fluconazole.

Adrenal insufficiency relating to concomitant treatment with Prednisone is described in section 4.5 The effect of fluconazole on other medicinal products.

### Tinea capitis

Fluconazole has been studied for treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Diflucan should not be used for *tinea capitis*.

#### Cryptococcosis

The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.

#### Deep endemic mycoses

The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as *paracoccidioidomycosis*, *lymphocutaneous sporotrichosis* and *histoplasmosis* is limited, which prevents specific dosing recommendations.

#### Halofantrine

Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended (see section 4.5).

#### Cytochrome P450

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Diflucan treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).

#### Terfenadine

The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine

should be carefully monitored (see sections 4.3 and 4.5).

#### Excipients

The Tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption. The product intended for pharmacy availability without prescription will carry a leaflet which will advise the patient: **Do not use Fluconazole Tablets 50mg/100mg/150mg/200mg without first consulting your doctor:-**

If you are under 16 or over 60 years of age.

If you are allergic to any of the ingredients in Fluconazole Tablets 50mg/100mg/150mg/200mg or other antifungals and other thrush treatments.

If you are taking any medicine other than the contraceptive pill.

If you are taking the antihistamine terfenadine or the prescription medicine cisapride, pimozide, quinidine and erythromycin.

If you have had thrush more than twice in the last six months.

If you have any disease or illness affecting your liver or kidneys or have had unexplained jaundice.

If you suffer from heart disease including heart rhythm problems.

If you have abnormal levels of potassium, calcium or magnesium in your blood.

If you develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).

If you develop signs of 'adrenal insufficiency' where the adrenal glands do not produce adequate amounts of certain steroid

hormones such as cortisol (chronic, or long lasting fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain).

If you or your partner have had exposure to a sexually transmitted disease.

If you are unsure about the cause of your symptoms.

*Women only:*

If you are pregnant, suspect you might be pregnant or are breast feeding.

If you have any abnormal or irregular vaginal bleeding or a blood stained discharge.

If you have vulval or vaginal sores, ulcers or blisters.

If you are experiencing lower abdominal pain or burning on passing urine.

*Men only:*

If your sexual partner does not have vaginal thrush.

If you have penile sores, ulcers or blisters.

If you have an abnormal penile discharge (leakage).

If your penis has started to smell.

If you have pain on passing urine.

The product should never be used again if the patient experiences a rash or anaphylaxis follows the use of the drug.

Recurrent use (men and women): Patients should be advised to consult their physician if the symptoms have not been relieved within one week of taking Fluconazole Tablets 50mg/100mg/150mg/200mg. A further Tablet can be used if the candidal infection returns after 7 days. However, if the candidal infection recurs more than twice within six months, patients should be advised to consult their physician.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose fluconazole 150mg has not yet been established:

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. 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. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

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

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 (see section 4.3).

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsade de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

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. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3)

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

Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be taken when both drugs are combined, notably with high dose fluconazole (800mg).

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine 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 (see section 4.4).

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

### **The effect of other medicinal products on fluconazole**

Hydrochlorothiazide: In a pharmacokinetic 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.

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.

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

### **The effect of fluconazole on other medicinal products**

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).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC<sub>10</sub> increased 2-fold, probably through 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 *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole 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. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione

anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

Benzodiazepines (Short acting). i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. 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.

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 calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil 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.

Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and

celecoxib (200 mg) the celecoxib C<sub>max</sub> and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

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

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patient should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

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.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment

with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

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

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

Methadone: Fluconazole may enhance the serum concentration of methadone.

Dosage of adjustment methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C<sub>max</sub> 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 co-administered 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.

Oral contraceptives: Two pharmacokinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on hormone level in a 50 mg fluconazole study, while at 200 mg daily the AUCs of ethinyl estradiol 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.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC<sub>24</sub> by 75% and  $C_{min}$  by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy

with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to 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.

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

Sulphonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (e.g., chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulphonylurea dosage is recommended during coadministration.

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.

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.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in  $C_{max}$  and AUC of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases  $C_{max}$  and AUC of zidovudine by 84% and 74%, 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.

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.

Ivacaftor: Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were being treated for at least three or more months with high dose (400-800 mg/daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole and these events is unclear.

Studies in animals shown reproductive toxicity (see section 5.3).

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

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding Fluconazole is found in human breast milk at lower concentrations than those in plasma, Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

#### Fertility

Fluconazole did not affect the fertility of male or female rats (see section 5.3)

#### **4.7 Effects on ability to drive and use machines**

No studies have been performed on the effects of Fluconazole on the ability to drive or use machines.

Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Fluconazole and should be advised not to drive or operate machines if any of these symptoms occur.

#### **4.8 Undesirable effects**

The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

The following adverse reactions 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):

System Order Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
	Uncommon	Anaemia
Immune system disorders	Rare	Anaphylaxis
Metabolism & nutrition disorders	Uncommon	Decreased Appetite
	Rare	Hypertriglyceridaemia, Hypercholesterolaemia Hypokalaemia
Psychiatric disorders	Uncommon	Insomnia, somnolence
Nervous system disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, taste perversion
	Rare	Tremor

Ear & labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Rare	Torsade de pointes (see section 4.4), QT Prolongation (see section 4.4)
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, vomiting
	Uncommon	Constipation dyspepsia, flatulence, dry mouth
Hepatobiliary disorders	Common	Alanine aminotransferase Increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)
	Uncommon	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin Increased (see section 4.4)
	Rare	Hepatic failure (see section 4.4), hepatocellular Necrosis (see section 4.4), hepatitis, hepatocellular damage (see section 4.4)
Skin & subcutaneous	Common	Rash (see section 4.4)

Sensory disorders	Uncommon	Pruritus, urticaria (see section 4.4), increased sweating, drug eruption* (see section 4.4)
	Rare	Toxic epidermal necrolysis (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematouspustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal, connective tissue & bone disorders	Uncommon	Myalgia
General & administration site disorders	Uncommon	Fatigue, malaise, asthenia, fever

\* including Fixed Drug Eruption

### Paediatric Population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication are comparable to those seen in adults.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

#### **4.9 Overdose**

There have been reports of overdosage with fluconazole and hallucination and paranoid behaviour have been concomitantly reported

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**

Pharmacotherapeutic group: Antimycotics for systemic use – triazole derivatives,

#### Mechanism of action

Fluconazole, a member of the triazole class of antifungal agents. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole.

Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg 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 50 mg do not affect its metabolism.

#### Susceptibility *in vitro*:

*In vitro*, fluconazole displays antifungal activity against most clinically common *Candida* species (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C. glabrata* shows a wide range of susceptibility while *C. krusei* is resistant to fluconazole.

Fluconazole also exhibits activity *in vitro* against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatiditis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

#### Pharmacokinetic/pharmacodynamic relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for

infections caused by strains with a higher fluconazole MIC.

Mechanisms of resistance

*Candida* spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

There have been reports 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.

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

S = Susceptible, R = Resistant

A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended

Antifungal	Species-related breakpoints (S≤/R>)					Non-species related breakpoints <sup>A</sup> S≤/R>
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida krusei</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	
Fluconazole	2/4	IE	--	2/4	2/4	2/4

as the species is a poor target for therapy with the medicinal product.

IE = There is insufficient evidence that the species in question is a good target for therapy with the medicinal product

**5.2 Pharmacokinetic properties**

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

Absorption

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

multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady state level by day 2.

### Distribution

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

Fluconazole achieves good penetration 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 concentration 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 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

### Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section

4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

### Elimination

Plasma elimination half-life for fluconazole is approximately 30 hours. 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 vaginal candidiasis, once daily and once weekly dosing for other indications.

### Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR < 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

### Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg•h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher

fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

#### Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The  $C_{max}$  was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was  $76.4 \pm 20.3$  µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Co-administration of diuretics did not

significantly alter AUC or  $C_{max}$ . In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

#### **5.3 Preclinical safety data**

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

#### Reproductive Toxicity

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.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg to 320mg/kg embryoletality in rats was increased and foetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. 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. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

### 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 (approximately 27 times the recommended human dose). 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 *Salmonella 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 1000µg/ml) showed no evidence of chromosomal mutations.

## **6. PHARMACEUTICAL PARTICULARS**

a) Each tablet contains:

Fluconazole USP	50mg
Excipients	q.s.

b) Each tablet contains:

Fluconazole USP	100mg
Excipients	q.s.

c) Each tablet contains:

Fluconazole USP	150mg
Excipients	q.s.

d) Each tablet contains:

Fluconazole USP	200mg
Excipients	q.s.

### **6.1 List of excipients**

Tablet content: Lactose, Pregelatinised, Maize Starch, Sodium Laurilsulfate, Colloidal Anhydrous Silica, Magnesium Stearate, Purified Talc

Tablet shell composition: Gelatin, Brilliant blue, Titanium Dioxide, Water, Sodium Laurilsulfate

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years

### **6.4 Special precautions for storage**

Do not store above 25°C.

### **6.5 Nature and contents of container**

PVC/PVDC/Al blisters.

*Pack sizes:* Blisters: 7, 14, 28, 30, 50, 90, 100 and 500mg modified-release tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

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

## **7. MANUFACTURED IN INDIA BY:**

### **TAJ PHARMACEUTICALS LTD.**

Mumbai, India

Unit No. 214.Old Bake House,  
Maharashtra chambers of Commerce Lane,  
Fort, Mumbai - 400001  
at:Gujarat, INDIA.

Customer Service and Product Inquiries:  
1-800-TRY-FIRST (1-800-222-434 & 1-800-222-825)

Monday through Saturday 9:00 a.m. to 7:00 p.m. EST

E-mail: [tajgroup@tajpharma.com](mailto:tajgroup@tajpharma.com)