

PRODUCT MONOGRAPH

<sup>Pr</sup>TEVA-FLUCONAZOLE  
Fluconazole Tablets  
Teva Standard  
50mg and 100 mg

<sup>Pr</sup>FLUCONAZOLE INJECTION  
Solution for Intravenous Infusion  
2 mg/mL  
(100 mL vial; and 100 mL and 200 mL Cryovac bags)

Antifungal Agent

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### **THERAPEUTIC CLASSIFICATION**

Antifungal

### **ACTION AND CLINICAL PHARMACOLOGY**

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.

A randomized, blinded, two-period, two-treatment, crossover bioequivalence study of TEVA-FLUCONAZOLE 100 mg tablets (Teva Canada Ltd.) and DIFLUCAN<sup>®</sup> (Fluconazole) 100 mg tablets (Pfizer Canada, Canada) administered as a single 2 x 100 mg dose was conducted in healthy male subjects (n=16) under fasting conditions. The results from the measured data are summarized in the table below.

**Table 1**

<i>Fluconazole (2 x 100 mg) From measured data</i>						
<i>Geometric Mean Arithmetic Mean (CV %)</i>						
<i>Parameter</i>	<i>Test</i> <sup>*</sup>		<i>Reference</i> <sup>†</sup>		<i>% Ratio of Geometric Means</i>	<i>90% Confidence Interval</i>
<i>AUC<sub>T</sub> (mcg·hr/mL)</i>	192.65		185.88		103.64	100.27-107.12
	193.84	(11.25)	186.59	(8.70)		
<i>AUC<sub>0-72</sub> (mcg·hr/mL)</i>	151.14		145.44		103.92	100.51-107.44
	151.85	(10.08)	145.83	(7.44)		
<i>AUC<sub>1</sub> (mcg·hr/mL)</i>	202.17		195.70		103.31	99.89-106.84
	203.50	(11.61)	196.37	(8.35)		
<i>C<sub>max</sub> (mcg/mL)</i>	4.34		4.32		100.49	95.52-105.71
	4.38	(12.47)	4.39	(17.65)		
<i>T<sub>max</sub><sup>§</sup> (h)</i>	1.31	(71.44)	1.86	(79.77)		
<i>T<sub>1/2</sub><sup>§</sup> (h)</i>	36.37	(13.33)	36.78	(11.20)		

\* Teva-Fluconazole 100 mg tablet (Teva Canada Ltd).

† Diflucan® (fluconazole) 100 mg tablets (Pfizer Canada Inc., Canada) were purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only

## INDICATIONS AND CLINICAL USE

### Treatment

TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) are indicated for the treatment of:

1. Oropharyngeal and esophageal candidiasis. Fluconazole is also effective for the treatment of serious systemic candidal infections, including urinary tract infection, peritonitis and pneumonia.
2. Cryptococcal meningitis.
3. Prevention of the recurrence of cryptococcal meningitis in patients with acquired immunodeficiency syndrome (AIDS).

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. 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.

Prophylaxis:

TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) are also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

### **CONTRAINDICATIONS**

TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) are contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients or to relatedazole compounds.

Co-administration of terfenadine is contraindicated in patients receiving TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) at multiple doses of 400 mg 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 metabolized via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine are contraindicated in patients receiving fluconazole. (see PRECAUTIONS – Drug Interactions).

### **WARNINGS**

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

**Hepatic injury: Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Fluconazole hepatotoxicity has usually, but not always been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION therapy should be monitored for the development of more severe hepatic injury. TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole.**

Fluconazole should be administered with caution to patients with renal dysfunction (see **DOSAGE and ADMINISTRATION-Impaired Renal Function**).

Anaphylaxis: In rare cases, anaphylaxis has been reported.

Dermatologic: Patients have rarely developed exfoliative skin disorders during treatment with

fluconazole. In patients with serious underlying diseases (predominantly AIDS and malignancy), those have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION should be monitored closely and the drug discontinued if lesions progress.

### **Use in Pregnancy**

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus.

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

There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400 mg/day to 800 mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). Exposure to fluconazole began during the first trimester in all cases and continued for three months or longer.

Case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high-dose (400-800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogyposis, and congenital heart disease.

These reported anomalies are similar to those seen in animal studies (see **TOXICOLOGY, Reproduction and Teratology**).

### **Use in Women of Child-bearing Potential**

Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period with TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION and for approximately 1 week (5 to 6 half-lives) after the final dose.

## **PRECAUTIONS**

### **QT Prolongation**

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on an electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions. (see **PRECAUTIONS - Drug Interactions – Drugs prolonging the QTc interval** and **ADVERSE REACTIONS**).

#### **CYP2C9, CYP2C19 and CYP3A4 metabolized drugs**

Fluconazole is a potent CYP2C9 and CYP2C19 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP 3A4 should be monitored (see **CONTRAINDICATIONS**).

#### **Use in Nursing Mothers**

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

#### **Use in Children**

An open-label, randomized, controlled trial has shown fluconazole to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age.

In a non-comparative study of children with serious systemic fungal infections, fluconazole was effective in the treatment of candidemia (10 of 11 patients cured) and disseminated candidiasis (5 of 6 patients cured or improved).

Fluconazole was effective for the suppression of cryptococcal meningitis and/or disseminated cryptococcal infection in a group of 6 children treated in a compassionate study of fluconazole for the treatment of life-threatening or serious mycosis. There is no information regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children.

In addition, the use of fluconazole in children with cryptococcal meningitis, candidal esophagitis or systemic candidal infections is consistent with the approved use of fluconazole in similar indications for adults, and is supported by pharmacokinetic studies in children (see **PHARMACOLOGY**) establishing dose proportionality between children and adults (see **DOSAGE AND ADMINISTRATION**).

The safety of fluconazole in children has been established in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1616 days (see **ADVERSE REACTIONS**).

Efficacy of fluconazole has not been established in infants less than 6 months of age. A small number of patients (29) ranging in age from 1 day to 6 months have been treated safely with fluconazole.

#### **Use in Elderly**

Fluconazole was well tolerated by patients aged 65 years and over.

Fluconazole is primarily cleared by renal excretion as unchanged drug. Because elderly patients

are more likely to have decreased renal function, caution should be exercised and dose adjusted based on creatinine clearance. It may be useful to monitor renal function.

In a small number of elderly patients with bone marrow transplant (BMT) in which fluconazole was administered prophylactically there was a greater incidence of drug discontinuation due to adverse reactions (4.3%) than in younger patients (1.7%).

### **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.

### **Superinfections**

Development of resistance to fluconazole has not been studied; however, 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.

As for other anti-infectives used prophylactically, prudent medical practice dictates that TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION be used judiciously in prophylaxis, in view of the theoretical risk of emergence of resistant strains.

### **Drug Interactions**

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9, 2C19 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, CYP2C19 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.

Clinically or potentially significant drug interactions between fluconazole and the following agents/classes have been observed:

- Alfentanil
- Amitriptyline/Nortriptyline
- Amphotericin B
- Azithromycin
- Benzodiazepines (Short Acting)
- Carbamazepine
- Calcium Channel Blockers
- Celecoxib
- Cimetidine
- Coumarin-Type Anticoagulants
- Cyclosporine
- Cyclophosphamide
- Drugs prolonging QTc interval: Astemizole, Cisapride, Terfenadine, Pimozide, Quinidine,

Erythromycin  
Fentanyl  
Halofantrine  
HMG-CoA reductase inhibitors  
Hydrochlorothiazide  
Losartan  
Methadone  
Non-steroidal anti-inflammatory drugs  
Oral Contraceptives  
Oral Hypoglycemics  
Phenytoin  
Prednisone  
Rifabutin  
Rifampin  
Saquinavir  
Sirolimus  
Sulfonylureas  
Tacrolimus  
Theophylline  
Tofacitinib  
Triazolam  
Vinca Alkaloids  
Vitamin A  
Zidovudine  
Voriconazole (CYP2C9, CYP2C19 and CYP3A4 Inhibitors)

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

#### 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 (see **DRUG INTERACTION STUDIES**).

#### Benzodiazepines (Short Acting)

Following oral or intravenous 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 short-acting benzodiazepines, which are metabolized by the cytochrome P450 system, are concomitantly administered with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored. (see DRUG INTERACTION STUDIES).

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%,  $C_{max}$  by 20 to 32%, and increases  $t_{1/2}$  by 25 to 50% due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

#### 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  $C_{max}$  and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole. Caution should be exercised and patients should be monitored for increased toxicity of celecoxib as well as careful monitoring of celecoxib associated adverse events.

#### Cimetidine

Absorption of orally administered fluconazole does not appear to be affected by gastric pH. Fluconazole 100 mg was administered as a single oral dose alone and two hours after a single dose of cimetidine 400 mg to six healthy male volunteers. After the administration of cimetidine, there was a significant decrease in fluconazole AUC (area under the plasma concentration-time curve) and  $C_{max}$ . There was a mean  $\pm$  SD decrease in fluconazole AUC of 13 %  $\pm$  11 % (range: -3.4 to -31%) and  $C_{max}$  decreased 19 %  $\pm$  14 % (range: -5 to -40 %). However, the administration of cimetidine 600 mg to 900 mg intravenously over a 4-hour period (from 1 hour before to 3 hours after a single oral dose of fluconazole 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in 24 healthy male volunteers (see **DRUG INTERACTION**

## STUDIES).

### Coumarin-Type Anticoagulants

Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. In post-marketing experience, as with some 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. Dose adjustments of warfarin may be necessary. Careful monitoring of prothrombin time in patients receiving TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) and coumarin-type anticoagulants is recommended (see **DRUG INTERACTION STUDIES**)

### Cyclosporine

Fluconazole may significantly increase the concentration and AUC of cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) and cyclosporine. This combination may be used by reducing the dosage of cyclosporine depending on cyclosporine concentration (see **DRUG INTERACTION STUDIES**).

### 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. Caution should be exercised and patients should be monitored for increased toxicity of cyclophosphamide.

### Tofacitinib

Exposure is increased when tofacitinib is coadministered with medications that result in both moderate inhibition of CYP3A4 and inhibition of CYP2C19 (e.g., fluconazole).

### Drugs prolonging the QTc interval:

The use of fluconazole in patients concurrently taking drugs metabolized by the Cytochrome P-450 system may be associated with elevations in the serum levels of these drugs. In the absence of definitive information caution should be used when co-administering fluconazole and such agents (see **PRECAUTIONS – QT Prolongation**). Patients should be carefully monitored.

### **Concomitant use of the following other medicinal products is contraindicated:**

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsade de pointes. Co-administration of fluconazole and astemizole is contraindicated (see **CONTRAINDICATIONS**).

Cisapride: There have been reports of cardiac events including torsade 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 QTc interval. Co-administration of cisapride is contraindicated in patients receiving TEVA-

FLUCONAZOLE and FLUCONAZOLE INJECTION (see **CONTRAINDICATIONS** and **DRUG INTERACTION STUDIES**).

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. In one study, 6 healthy volunteers received terfenadine 60 mg BID for 15 days. One study at 200 mg daily dose of fluconazole failed to demonstrate a prolongation of QTc interval. However, 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. Therefore the combined use of fluconazole at doses of 400 mg or higher with terfenadine is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTION STUDIES**). Patients should be carefully monitored if they are being concurrently prescribed TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) at multiple doses lower than 400 mg/day with terfenadine.

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 **PRECAUTIONS**).

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

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsade de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see **CONTRAINDICATIONS**). In a large cohort of patients, the multivariate adjusted rate of sudden death from cardiac causes was five times as high among those who concurrently used CYP3A inhibitors and erythromycin compared with those who had used neither CYP3A inhibitors nor any of the study antibiotic medications.

#### 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. Patient should be monitored for serious adverse effects such as respiratory depression.

#### Halofantrine

Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Caution should be exercised and patients should be monitored for increased

toxicity of halofantrine.

#### 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 creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

#### Hydrochlorothiazide

In a pharmacokinetic interaction study, coadministration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects received concomitant diuretics (see **DRUG INTERACTION STUDIES**).

#### 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 adjustment of methadone may be necessary.

#### Non-steroidal anti-inflammatory drugs

The  $C_{max}$  and AUC of flurbiprofen were 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] were 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 non-steroidal anti-inflammatory drugs (NSAIDs) that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

#### Oral Contraceptives

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

contraceptive (see **DRUG INTERACTION STUDIES**).

#### Oral Hypoglycemics

Clinically significant hypoglycemia may be precipitated by the use of fluconazole with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined fluconazole and glyburide use. Fluconazole reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary (see **DRUG INTERACTION STUDIES**).

#### Phenytoin

Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended (see **DRUG INTERACTION STUDIES**).

#### 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

There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored (see **DRUG INTERACTION STUDIES**).

#### Rifampin

Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) when it is administered with rifampin (see **DRUG INTERACTION STUDIES**).

#### Saquinavir

Fluconazole increases the AUC of saquinavir by approximately 50%,  $C_{max}$  by approximately 55% and decreases clearance of saquinavir by approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary. Caution should be exercised and patients should be monitored for increased toxicity of saquinavir.

#### 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. Caution should be exercised and patients should be monitored for increased toxicity of sirolimus.

#### Sulfonylureas

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

#### Tacrolimus

Fluconazole significantly increases the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4. Increased levels of tacrolimus have been associated with nephrotoxicity. Dosage adjustment of tacrolimus should be made depending on tacrolimus concentration. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored for tacrolimus associated adverse effects, especially nephrotoxicity. (see **DRUG INTERACTION STUDIES**).

#### 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 TEVA-FLUCONAZOLE or FLUCONAZOLE INJECTION (fluconazole), and therapy modified appropriately if signs of toxicity develop. TEVA-FLUCONAZOLE or FLUCONAZOLE INJECTION (fluconazole) increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving fluconazole and theophylline is recommended (see **DRUG INTERACTION STUDIES**).

#### Triazolam

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%,  $C_{max}$  with 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. Caution should be exercised and patients should be monitored for increased toxicity of triazolam.

#### 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. Caution should be exercised and patients should be monitored for increased toxicity of vinca alkaloids (e.g. vincristine and vinblastine).

#### Vitamin A

Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, central nervous system (CNS) related undesirable effects have developed in the form of pseudotumour cerebri, which

disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

#### Zidovudine

Fluconazole increases C<sub>max</sub> and AUC of zidovudine by 84% and 74%, respectively, due to an approximately 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 (see **DRUG INTERACTION STUDIES**).

#### Voriconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitors)

Avoid concomitant administration of voriconazole and fluconazole at any dose. Monitor for adverse events and toxicity related to voriconazole; especially, if voriconazole is started within 24 h after the last dose of fluconazole. (see **DRUG INTERACTION STUDIES**.)

Interaction studies with other medications have not been conducted, but such interactions may occur.

#### Drug/Laboratory Test Interactions

None known.

### ADVERSE REACTIONS

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

#### **In Patients Receiving a Single Dose for Vaginal Candidiasis:**

During comparative clinical studies conducted in the United States, 448 patients with vaginal candidiasis were treated with fluconazole, 150 mg single dose. The overall incidence of side effects possibly related to fluconazole was 26%. In 422 patients receiving active comparative agents, the incidence was 16%. The most common treatment-related adverse events reported in the patients who received 150 mg single dose fluconazole for vaginitis were headache (13%), nausea (7%), and abdominal pain (6%). Other side effects reported with an incidence equal to or greater than 1% included diarrhea (3%), dyspepsia (1%), dizziness (1%), and taste perversion (1%). Most of the reported side effects were mild to moderate in severity. Rarely, angioedema and anaphylactic reaction have been reported in marketing experience.

#### ADULTS:

Sixteen percent of over 4000 patients treated with fluconazole in clinical trials of 7 days or more experienced adverse events.

Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

Adverse clinical events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%). However, the patterns of adverse events 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%).

The two most serious adverse clinical events noted during clinical trials with fluconazole were:

1. Exfoliative skin disorders
2. Hepatic necrosis

Because most of these patients had serious underlying disease (predominantly AIDS or malignancy) and were receiving multiple concomitant medications, including many known to be hepatotoxic or associated with exfoliative skin disorders, the causal association of these reactions with fluconazole is uncertain. Two cases of hepatic necrosis and one exfoliative skin disorder (Stevens-Johnson syndrome) were associated with a fatal outcome (see WARNINGS).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4,048 patients receiving fluconazole for seven (7) or more days in clinical trials:

Central and Peripheral Nervous System: headache (1.9%)

Dermatologic: skin rash (1.8%)

Gastrointestinal: abdominal pain (1.7%), diarrhea (1.5%), nausea (3.7%) and vomiting (1.7%).

Hepato-biliary disorders: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased.

Other treatment-related clinical adverse events which occurred less commonly (0.2 to <1%) are presented by organ system below:

Skin and Appendages: pruritus, urticaria, drug eruption.

Musculoskeletal: myalgia.

Central and Peripheral Nervous System: convulsions, dizziness, paresthesia, tremor, vertigo, seizures.

Autonomic Nervous System: dry mouth, increased sweating.

Psychiatric: insomnia, somnolence.

Gastrointestinal: anorexia, constipation, dyspepsia, flatulence.

Liver and Biliary System: cholestasis, bilirubin increased, jaundice.

Special Senses: taste perversion.

Hematopoietic: anemia.

General: fatigue, malaise, asthenia, fever.

Immunologic: In rare cases, anaphylaxis has been reported.

*Hepatobiliary:* In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with fluconazole. (see **WARNINGS**.) The spectrum of



these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. 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. 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 clinical trials. These elevations occurred in 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: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

### **Post-Marketing Experience**

In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post-marketing experience):

Cardiovascular: QT prolongation, torsade de pointes (see **PRECAUTIONS – QT Prolongation**).

Body As A Whole: Asthenia, fatigue, fever, malaise and urticaria.

Central Nervous System: Seizures, dizziness.

Dermatologic: alopecia, acute generalized exanthematous-pustulosis, face edema, exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necrolysis, dermatitis exfoliative (see **WARNINGS**), drug eruption, increased sweating.

Gastrointestinal: Cholestasis, dry mouth, hepatocellular damage, dyspepsia, vomiting.

Hematopoietic and Lymphatic: Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.

Immunologic: In rare cases, anaphylaxis including angioedema, face edema, and pruritus.

Liver/Biliary: Hepatic toxicity, including rare cases of fatalities, hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage.

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Musculoskeletal: Myalgia.

Nervous System: Tremor, insomnia, paresthesia, somnolence, vertigo.

Other Senses: Taste perversion.

### **Laboratory Test Abnormalities**

#### **Liver Function**

Clinically significant increases were observed in the following proportions of patients: AST 1%, ALT 1.2%, alkaline phosphatase 1.2%, total bilirubin 0.3%. The incidence of elevated serum aminotransferases was independent of age or route (p.o. or i.v.) of administration but was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid or oral hypoglycemic agents. Clinically significant

increases also were more frequent in patients who: 1) had AST or ALT elevations greater than three times the upper limit of normal (>3 x ULN) at the time of entering the study (baseline), 2) had a diagnosis of hepatitis at any time during the study and, 3) were identified as alcohol abusers. The overall rate of serum aminotransferase elevations of more than 8 times the upper limit of normal was approximately 1% in patients treated with fluconazole during clinical trials (see Table 2).

**Table 2**

Lab Parameter	*Number of Patients	% Abnormal	*Number of Patients	% Abnormal
		Baseline >3 x ULN		Baseline < 3 X ULN
AST	53	9.4	3007	4.2
ALT	65	3.1	2874	4.8
		Hepatitis Patients		Non-Hepatitis Patients
AST	160	10.6	2900	3.9
ALT	140	11.4	2799	4.4
		Alcohol Abuse		Non-Alcohol Abuse
AST	42	9.5	3018	4.2
ALT	40	10.0	2899	4.7
		Received I.V. Fluconazole		Never Received I.V. Fluconazole
AST	144	5.6	2916	4.2
ALT	139	5.0	2800	4.7
		≥ 65 Years Old		< 65 Years Old
AST	277	4.3	2783	4.3
ALT	258	3.9	2681	4.8

\*Note: Only patients who had measurements at baseline and during therapy were included.

#### Renal Function

Clinically significant increases were observed in the following proportions of patients: blood urea nitrogen (0.4%) and creatinine (0.3%).

#### Hematological Function

Clinically meaningful deviations from baseline in hematologic values which were possibly related to fluconazole were observed in the following proportions of patients: hemoglobin (0.5%), white blood cell count (0.5%) and total platelet count (0.6%).

#### **CHILDREN:**

The pattern and incidence of adverse events and laboratory abnormalities recorded during pediatric clinical trials are comparable to those seen in adults.

In Phase II/III clinical trials conducted in the United States and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with fluconazole at doses ranging up to 15 mg/kg/day for up to 1616 days. Thirteen percent of children experienced treatment-related adverse events. The most commonly reported events were vomiting (5.4%), abdominal pain (2.8%), nausea (2.3%) and diarrhea (2.1%). Treatment was discontinued in 2.6% of patients due to adverse clinical events and in 1.0% of patients due to laboratory test abnormalities. The majority of treatment-related laboratory abnormalities were elevations of transaminases or alkaline phosphatase.

### Percentage of Patients With Treatment-Related Side Effects

	Fluconazole (N=577)	Comparative Agent (N=451)
With any side effect	13.0	9.3
Vomiting	5.4	5.1
Abdominal pain	2.8	1.6
Nausea	2.3	1.6
Diarrhea	2.1	2.2

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

**For management of a suspected drug overdose, please contact your regional Poison Control**

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

**Symptoms:** There have been reports of overdose with fluconazole accompanied by hallucination and paranoid behaviour.

**Treatment:** In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Fluconazole is largely excreted in urine. A three hour hemodialysis session decreases plasma levels by approximately 50%.

Mice and rats receiving very high doses of fluconazole, whether orally or intravenously, displayed a variety of nonspecific, agonal signs such as decreased activity, ataxia, shallow respiration, ptosis, lacrimation, salivation, urinary incontinence and cyanosis. Death was sometimes preceded by clonic convulsions.

### **DOSAGE AND ADMINISTRATION**

#### **Oral (tablets) and Intravenous Administration**

Fluconazole is well absorbed and excreted predominantly unchanged in urine following oral administration in humans. The oral bioavailability is essentially complete (greater than 90%) and is independent of dose. Peak plasma concentrations after oral administration are attained rapidly,

usually within two (2) hours of dosing. **Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral tablets and intravenous administration.** The terminal plasma elimination half-life is approximately 30 hours (range 20-50 hours).

The daily dose of fluconazole and the route of administration should be based on the infecting organism, the patient's condition and the response to therapy. Treatment should be continued until clinical parameters and laboratory tests indicate that an active fungal infection has been cured or has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

IN THE DOSING INSTRUCTIONS BELOW, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL (TABLETS) AND INTRAVENOUS ADMINISTRATION SINCE ORAL ABSORPTION IS RAPID AND ALMOST COMPLETE.

**RECOMMENDED DOSAGES IN ADULTS AND CHILDREN (also see PHARMACOLOGY):**

**TREATMENT**

**Loading Dose**

**Administration of a loading dose on the first day of treatment, consisting of twice the usual daily dose, results in plasma concentrations close to steady state by the second day. Patients with acute infections should be given a loading dose equal to twice the daily dose, not to exceed a maximum single dose of 400 mg in adults or 12 mg/kg in children, on the first day of treatment.**

Dosage Equivalency Scheme (see Table 3)

**Table 3**

<b>Pediatric Patients</b>	<b>Adults</b>
3 mg/kg	100 mg
6 mg/kg	200 mg
12 mg/kg*	400 mg

\* Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

**Table 4**

<b>Recommended Treatment Guidelines</b>		
<b>Indication</b>	<b>Adults</b>	<b>Children</b>
<b>Oropharyngeal Candidiasis</b>	100 mg once daily for at least 2 weeks to decrease the likelihood of relapse.	3 mg/kg once daily for at least 2 weeks to decrease the likelihood of relapse.
<b>Esophageal Candidiasis</b>	100 mg to 200 mg once daily for a minimum of 3 weeks, and for at least 2 weeks following resolution of symptoms.	3 mg/kg to 6 mg/kg once daily for a minimum of 3 weeks, and for at least 2 weeks following resolution of symptoms.
<b>Systemic Candidiasis (Candidemia and Disseminated Candidal Infections)</b>	200 mg to 400 mg once daily for a minimum of 4 weeks, and for at least 2 weeks following resolution of symptoms.	6 mg/kg to 12 mg/kg per day have been used in an open, non-comparative study of a small number of patients.
<b>Cryptococcal Meningitis</b>	200 mg to 400 mg once daily. The duration of therapy for cryptococcal meningitis is unknown, it is recommended that the initial therapy should last a minimum of 10 weeks.	6 mg/kg to 12 mg/kg once daily. The recommended duration for initial therapy is 10-12 weeks after the cerebrospinal fluid becomes culture-negative.
<b>Prevention of Recurrence of Cryptococcal Meningitis in Patients with AIDS</b>	200 mg once daily.	6 mg/kg once daily.

**Premature Neonates**

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns (see PHARMACOLOGY). Based upon the prolonged half-life seen in premature newborns (gestation age 26 to 29 weeks), these children, in the first two weeks of life, should receive the same dosage (mg/kg) as in older children, but administered every 72 hours. After the first two weeks, these children should be dosed once daily.

**Neonates**

No information regarding fluconazole pharmacokinetics in full-term newborns is available.

**Prophylaxis in Adult Patients**

The recommended fluconazole daily dosage for the prevention of candidiasis in adult patients undergoing bone marrow transplantation is 400 mg once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils per mm<sup>3</sup>) should start fluconazole prophylaxis several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells per mm<sup>3</sup>.

Fluconazole may be administered either orally or by intravenous infusion. The intravenous infusion of FLUCONAZOLE INJECTION should be administered at a maximum rate of approximately 200 mg/hour given as a continuous infusion (see DIRECTIONS FOR USE in PHARMACEUTICAL INFORMATION).

**Dosage in Patients with Impaired Renal Function****Adults:**

Fluconazole is cleared primarily by renal excretion as unchanged drug. In patients with impaired renal function, an initial loading dose of 50 to 400 mg should be given (for children, see below). After the loading dose, the daily dose (according to indication) should be administered as outlined in the following table:

**Table 5**

<u>CREATININE CLEARANCE</u> <u>(mL/min)</u> >50	<u>CREATININE CLEARANCE</u> <u>(mL/sec)</u> > 0.83	<u>PERCENT RECOMMENDED</u> <u>DOSE</u>
21-50 (no dialysis)	0.35-0.83 (no dialysis)	100%
11-20 (no dialysis)	0.18-0.34 (no dialysis)	50%
Regular hemodialysis	Regular hemodialysis	25%
		100% after each dialysis

Patients on regular dialysis should receive 100% of the recommended dose after each dialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance.

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight and age of the patient) should be used to estimate the creatinine clearance (see Table 6).

**Table 6**

<u>Creatinine Clearance Calculations</u>	
<u>mL/min</u>	<u>mL/sec</u>
Males: $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$	Males: $\frac{\text{Weight (kg)} \times (140 - \text{age})}{50 \times \text{serum creatinine (}\mu\text{ mol/L)}}$
Females: 0.85 x above value	Females: 0.85 x above value

**Children:**

Although the pharmacokinetics of fluconazole have not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults. The following formula may be used to estimate creatinine clearance in children:

$$K \times \frac{\text{linear length or height (cm)}}{\text{serum creatinine (mg/100 mL)}}$$

(where K = 0.55 for children older than 1 year and K = 0.45 for infants).

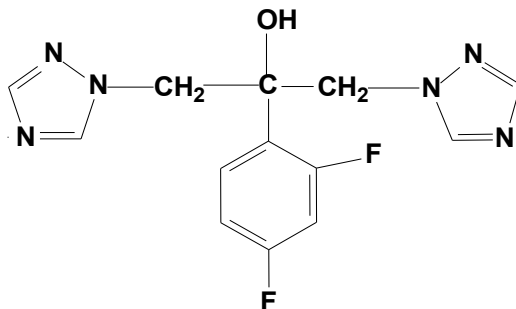
## PHARMACEUTICAL INFORMATION

### DRUG SUBSTANCE:

Proper Name: Fluconazole

Chemical Name: 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol

Structural Formula:



Molecular Formula: C<sub>13</sub>H<sub>12</sub>N<sub>6</sub>OF<sub>2</sub>

Molecular Weight: 306.27 g/mol

Description: Fluconazole is a white to off-white crystalline powder, freely soluble in methanol, soluble in acetone, sparingly soluble in aqueous 0.1N hydrochloric acid and ethanol, slightly soluble in isopropanol, water and aqueous 0.1 N sodium hydroxide and insoluble in hexane.

Fluconazole is a very weak base with a pK<sub>a</sub> of 1.76 at 24°C and as a consequence will be essentially nonprotonated at pH values above 3.5. Melting point is 140.3°C. The partition coefficient Log P=+0.5.

## **COMPOSITION**

TEVA-FLUCONAZOLE (tablets): Active ingredient: Each tablet contains 50 mg or 100 mg of fluconazole. Non-medicinal ingredients: dibasic calcium phosphate anhydrous, croscarmellose sodium, microcrystalline cellulose, FD & C Red #40 Aluminum Lakes (alumina hydrate base), povidone, colloidal silicon dioxide, and magnesium stearate.

FLUCONAZOLE INJECTION: Each mL of the sterile solution for intravenous injection contains 2 mg of fluconazole, 9 mg of sodium chloride (isotonicity), and Water for Injection, q.s. 1 mL.

## **STABILITY AND STORAGE RECOMMENDATION**

TEVA-FLUCONAZOLE (tablets): Store bottles between 15°C - 30°C.

FLUCONAZOLE INJECTION: Store vials between 15°C - 30°C. Store bags between 5°C - 25°C. Do not freeze.

## **DIRECTIONS FOR USE**

### **FLUCONAZOLE INJECTION**

#### Vials:

Inspect visually for particulate matter or discoloration prior to administration. Do not use if cloudiness or precipitation is evident.

Reject the contents as unsterile if the metal seal is broken. NOT INTENDED FOR MULTIDOSE USE: discard any unused portion when the seal is first broken.

Connect an intravenous giving set to the vial of FLUCONAZOLE INJECTION solution and also insert a venting set through the stopper. Infuse FLUCONAZOLE INJECTION for intravenous solution at a maximum rate of 200 mg/hour. Flush FLUCONAZOLE INJECTION intravenous solution remaining in the giving set with sterile normal saline. Because FLUCONAZOLE INJECTION is available as a dilute saline solution, consideration should be given to the rate of fluid administration in patients requiring sodium or fluid restriction.

#### Bags:

FLUCONAZOLE INJECTION in Cryovac flexible infusion bag with spike port is intended only for intravenous infusion using sterile equipment. The intravenous infusion of FLUCONAZOLE INJECTION should be administered at a maximum rate of approximately 200 mg/hour given as a continuous infusion.

Do not remove unit from overwrap until ready to use. The overwrap is a moisture barrier. The inner bag maintains the sterility of the product.



Inspect visually for particulate matter or discoloration prior to administration. Do not use if cloudiness or precipitation is evident or if the seal is not intact.

NOT INTENDED FOR MULTIDOSE USE: Single use. Discard any unused portion.

Connect an intravenous giving set to the container of fluconazole injection solution. Infuse fluconazole injection solution at a maximum rate of 200 mg/hour. Flush fluconazole intravenous solution remaining in the giving set with sterile normal saline. Because fluconazole is available as a dilute saline solution, consideration should be given to the rate of fluid administration in patients requiring sodium or fluid restriction.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed. Do not add supplemental medication.

### **Incompatibility**

It is recommended that FLUCONAZOLE INJECTION for intravenous infusion be infused separately.

### **Compatibility**

#### **Administration sets ("giving" sets).**

FLUCONAZOLE INJECTION for intravenous infusion is compatible with (i.e. not susceptible to absorption) sets constructed of a delivery tube (PVC) luer lock (modified phenylene oxide), flash ball (latex) drip chamber (polypropylene) and piercing spike (polypropylene).

## **AVAILABILITY OF DOSAGE FORMS**

TEVA-FLUCONAZOLE is available as a four-sided, pink 50 mg compressed tablet, containing 50 mg of fluconazole, engraved with 'N' on one side and '50' on the other. Supplied in bottles of 100.

TEVA-FLUCONAZOLE is available as a four-sided, pink 100 mg compressed tablet, containing 100 mg of fluconazole, engraved with 'N' on one side and '100' on the other. Supplied in bottles of 50.

FLUCONAZOLE INJECTION is available as a sterile aqueous solution for direct infusion. Each mL contains 2 mg fluconazole and 9 mg sodium chloride. Supplied in clear glass vials of 100 mL (1x100mL vial package), affording doses of 200 mg fluconazole, sealed with a rubber stopper. Also supplied in 100 ml (10 x 100 mL) and 200 mL (6 x 200 mL) Cryovac infusion bag.

## DRUG INTERACTION STUDIES

*Oral contraceptives:* Oral contraceptives were administered as a single dose both before and after the oral administration of fluconazole 50 mg once daily for 10 days in 10 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%) (see **PRECAUTIONS – Drug Interactions**).

In a second study, twenty-five normal females received daily doses of both 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. The order of study treatment was random. 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.

A third study evaluated the potential interaction of once weekly dosing of fluconazole 300 mg to 21 normal females taking an oral contraceptive containing ethinyl estradiol and norethindrone. In this placebo-controlled, double-blind, randomized, two-way crossover study carried out over three cycles of oral contraceptive treatment, fluconazole dosing resulted in small increases in the mean AUCs of ethinyl estradiol and norethindrone compared to similar placebo dosing. The mean AUCs of ethinyl estradiol and norethindrone increased by 24% (95% C.I. range: 18-31%) and 13% (95% C.I. range: 8-18%), respectively, relative to placebo. Fluconazole treatment did not cause a decrease in the ethinyl estradiol AUC of any individual subject in this study compared to placebo dosing. The individual AUC values of norethindrone decreased very slightly (<5%) in 3 of the 21 subjects after fluconazole treatment.

*Cimetidine:* Fluconazole 100 mg was administered as a single oral dose alone and two hours after a single dose of cimetidine 400 mg to six healthy male volunteers. After the administration of cimetidine, there was a significant decrease in fluconazole AUC and  $C_{max}$ . There was a mean  $\pm$  SD decrease in fluconazole AUC of 13%  $\pm$  11% (range: –3.4 to –31%) and  $C_{max}$  decreased 19%  $\pm$  14% (range: –5 to –40%). However, the administration of cimetidine 600 mg to 900 mg intravenously over a four-hour period (from one hour before to 3 hours after a single oral dose of fluconazole 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in 24 healthy male volunteers (see **PRECAUTIONS – Drug Interactions**).

*Antacid:* Administration of Maalox® (20 mL) to 14 normal male volunteers immediately prior to a single dose of fluconazole 100 mg had no effect on the absorption or elimination of fluconazole.

*Hydrochlorothiazide:* Concomitant oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and  $C_{max}$  compared to fluconazole given alone. There was a mean  $\pm$  SD

increase in fluconazole AUC and  $C_{\max}$  of  $45\% \pm 31\%$  (range: 19 to 114%) and  $43\% \pm 31\%$  (range: 19 to 122%), respectively. These changes are attributed to a mean  $\pm$  SD reduction in renal clearance of  $30\% \pm 12\%$  (range:  $-10$  to  $-50\%$ ) (see **PRECAUTIONS – Drug Interactions**).

*Rifampin*: Administration of a single oral 200 mg dose of fluconazole after 15 days of rifampin administered as 600 mg daily in eight healthy male volunteers resulted in a significant decrease in fluconazole AUC and a significant increase in apparent oral clearance of fluconazole. There was a mean  $\pm$  SD reduction in fluconazole AUC of  $23\% \pm 9\%$  (range:  $-13$  to  $-42\%$ ). Apparent oral clearance of fluconazole increased  $32\% \pm 17\%$  (range: 16 to 72%). Fluconazole half-life decreased from  $33.4 \pm 4.4$  hours to  $26.8 \pm 3.9$  hours (see **PRECAUTIONS – Drug Interactions**).

*Warfarin*: There was a significant increase in prothrombin time response (area under the prothrombin time-time curve) following a single dose of warfarin (15 mg) administered to 13 normal male volunteers following oral fluconazole 200 mg administered daily for 14 days as compared to the administration of warfarin alone. There was a mean  $\pm$  SD increase in the prothrombin time response (area under the prothrombin time-time curve) of  $7\% \pm 4\%$  (range:  $-2$  to 13%). Mean is based on data from 12 subjects as one of 13 subjects experienced a 2-fold increase in his prothrombin time response.

*Phenytoin*: Phenytoin AUC was determined after 4 days of phenytoin dosing (200 mg daily, orally for 3 days followed by 250 mg intravenously for one dose) both with and without the administration of fluconazole (oral fluconazole 200 mg daily for 16 days) in 10 normal male volunteers. There was a significant increase in phenytoin AUC. The mean  $\pm$  SD increase in phenytoin AUC was  $88\% \pm 68\%$  (range: 16 to 247%). The absolute magnitude of this interaction is unknown because of the intrinsically nonlinear disposition of phenytoin (see **PRECAUTIONS – Drug Interactions**).

*Cyclosporine*: Cyclosporine AUC and  $C_{\max}$  were determined before and after the administration of fluconazole 200 mg daily for 14 days in eight renal transplant patients who had been on cyclosporine therapy for at least 6 months and on a stable cyclosporine dose for at least 6 weeks. There was a significant increase in cyclosporine AUC,  $C_{\max}$ ,  $C_{\min}$  (24-hour concentration), and a significant reduction in apparent oral clearance following the administration of fluconazole. The mean  $\pm$  SD increase in AUC was  $92\% \pm 43\%$  (range: 18 to 147%). The  $C_{\max}$  increased  $60\% \pm 48\%$  (range:  $-5$  to 133%). The  $C_{\min}$  increased  $157\% \pm 96\%$  (range: 33 to 360%). The apparent oral clearance decreased  $45\% \pm 15\%$  (range:  $-15$  to  $-60\%$ ) (see **PRECAUTIONS – Drug Interactions**).

*Zidovudine*: Plasma zidovudine concentrations were determined on two occasions (before and following fluconazole 200 mg daily for 15 days) in 13 volunteers with AIDS or ARC who were on a stable zidovudine dose for at least two weeks. There was a significant increase in zidovudine AUC following the administration of fluconazole. The mean  $\pm$  SD increase in AUC was  $20\% \pm 32\%$  (range:  $-27$  to 104%). The metabolite, GZDV, to parent drug ratio significantly decreased after the administration of fluconazole, from  $7.6 \pm 3.6$  to  $5.7 \pm 2.2$  (see **PRECAUTIONS – Drug Interactions**).

*Theophylline*: The pharmacokinetics of theophylline were determined from a single intravenous

dose of aminophylline (6 mg/kg) before and after the oral administration of fluconazole 200 mg daily for 14 days in 16 normal male volunteers. There were significant increases in theophylline AUC,  $C_{max}$ , and half-life with a corresponding decrease in clearance. The mean  $\pm$  SD theophylline AUC increased  $21\% \pm 16\%$  (range:  $-5$  to  $48\%$ ). The  $C_{max}$  increased  $13\% \pm 17\%$  (range:  $-13$  to  $40\%$ ). Theophylline clearance decreased  $16\% \pm 11\%$  (range:  $-32$  to  $5\%$ ). The half-life of theophylline increased from  $6.6 \pm 1.7$  hours to  $7.9 \pm 1.5$  hours (see **PRECAUTIONS – Drug Interactions**).

*Terfenadine*: Six healthy volunteers received terfenadine 60 mg BID for 15 days. Fluconazole 200 mg was administered daily from days 9 through 15. Fluconazole did not affect terfenadine plasma concentrations. Terfenadine acid metabolite AUC increased  $36\% \pm 36\%$  (range: 7 to  $102\%$ ) from day 8 to day 15 with the concomitant administration of fluconazole. There was no change in cardiac repolarization as measured by Holter QTc intervals. 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 (see **CONTRAINDICATIONS and PRECAUTIONS – Drug Interactions**).

*Oral Hypoglycemics*: The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycemic agents tolbutamide, glipizide, and glyburide were evaluated in three placebo-controlled studies in normal volunteers. All subjects received the sulfonylurea alone as a single dose and again as a single dose following the administration of fluconazole 100 mg daily for 7 days. In these three studies, 22/46 (47.8%) of fluconazole treated patients and 9/22 (40.1%) of placebo-treated patients experienced symptoms consistent with hypoglycemia (see **PRECAUTIONS – Drug Interactions**).

*Tolbutamide*: In 13 normal male volunteers, there was significant increase in tolbutamide (500 mg single dose) AUC and  $C_{max}$  following the administration of fluconazole. There was a mean  $\pm$  SD increase in tolbutamide AUC of  $26\% \pm 9\%$  (range: 12 to  $39\%$ ). Tolbutamide  $C_{max}$  increased  $11\% \pm 9\%$  (range:  $-6$  to  $27\%$ ) (see **PRECAUTIONS – Drug Interactions**).

*Glipizide*: The AUC and  $C_{max}$  of glipizide (2.5 mg single dose) were significantly increased following the administration of fluconazole in 13 normal male volunteers. There was a mean  $\pm$  SD increase in AUC of  $49\% \pm 13\%$  (range: 27 to  $73\%$ ) and an increase in  $C_{max}$  of  $19\% \pm 23\%$  (range:  $-11$  to  $79\%$ ) (see **PRECAUTIONS – Drug Interactions**).

*Glyburide*: The AUC and  $C_{max}$  of glyburide (5 mg single dose) were significantly increased following the administration of fluconazole in 20 normal male volunteers. There was a mean  $\pm$  SD increase in AUC of  $44\% \pm 29\%$  (range:  $-13$  to  $115\%$ ) and  $C_{max}$  increased  $19\% \pm 19\%$  (range:  $-23$  to  $62\%$ ). Five subjects required oral glucose following the ingestion of glyburide after 7 days of fluconazole administration (see **PRECAUTIONS – Drug Interactions**).

*Rifabutin*: There have been published reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin (see **PRECAUTIONS – Drug Interactions**).

*Tacrolimus*: There have been published reports that an interaction exists when fluconazole is

administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. (see **PRECAUTIONS – Drug Interactions**).

*Cisapride*: A placebo-controlled, randomized, multiple-dose study examined the potential interaction of fluconazole with cisapride. Two groups of 10 normal subjects were administered fluconazole 200 mg daily or placebo. Cisapride 20 mg four times daily was started after 7 days of fluconazole or placebo dosing. Following a single dose of fluconazole, there was a 101% increase in the cisapride AUC and a 91% increase in the cisapride  $C_{max}$ . Following multiple doses of fluconazole, there was a 192% increase in the cisapride AUC and a 154% increase in the cisapride  $C_{max}$ . Fluconazole significantly increased the QTc interval in subjects receiving cisapride 20 mg four times daily for 5 days (see **CONTRAINDICATIONS** and **PRECAUTIONS – Drug Interactions**).

*Midazolam*: The effect of fluconazole on the pharmacokinetics and pharmacodynamics of midazolam was examined in a randomized, cross-over study in 12 volunteers. In the study, subjects ingested placebo or 400 mg fluconazole on Day 1 followed by 200 mg daily from Day 2 to Day 6. In addition, a 7.5 mg dose of midazolam was orally ingested on the first day, 0.05 mg/kg was administered intravenously on the fourth day, and 7.5 mg orally on the sixth day. Fluconazole reduced the clearance of IV midazolam by 51%. On the first day of dosing, fluconazole increased the midazolam AUC and  $C_{max}$  by 259% and 150%, respectively. On the sixth day of dosing, fluconazole increased the midazolam AUC and  $C_{max}$  by 259% and 74%, respectively. The psychomotor effects of midazolam were significantly increased after oral administration of midazolam but not significantly affected following intravenous midazolam. A second randomized, double-dummy, placebo-controlled, cross over study in three phases was performed to determine the effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. In each phase the subjects were given oral fluconazole 400 mg and intravenous saline; oral placebo and intravenous fluconazole 400 mg; and oral placebo and IV saline. An oral dose of 7.5 mg of midazolam was ingested after fluconazole/placebo. The AUC and  $C_{max}$  of midazolam were significantly higher after oral than IV administration of fluconazole. Oral fluconazole increased the midazolam AUC and  $C_{max}$  by 272% and 129%, respectively. IV fluconazole increased the midazolam AUC and  $C_{max}$  by 244% and 79%, respectively. Both oral and IV fluconazole increased the pharmacodynamic effects of midazolam (see **PRECAUTIONS – Drug Interactions**).

*Azithromycin*: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 800 mg oral dose of fluconazole on the pharmacokinetics of a single 1200 mg oral dose of azithromycin as well as the effects of azithromycin on the pharmacokinetics of fluconazole. There was no significant pharmacokinetic interaction between fluconazole and azithromycin (see **PRECAUTIONS – Drug Interactions**).

*Voriconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitors)*: Concurrent administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 6 healthy male subjects resulted in an increase in  $C_{max}$ , and AUC, of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow up on a clinical study involving 8 healthy subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect.

Concomitant administration of voriconazole and fluconazole at any dose is not recommended (see **PRECAUTIONS – Drug Interactions**).

## **MICROBIOLOGY**

Fluconazole is a polar *bis*-triazole antifungal agent which exhibits fungistatic activity *in vitro* against a variety of fungi and yeasts; it also exhibits fungistatic activity *in vivo* against a broad range of systemic and superficial fungal infections.

In common with other azole antifungal agents, most fungi show a higher apparent sensitivity to fluconazole *in vivo* than *in vitro*. 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 and in immunocompromised animals; with *Cryptococcus neoformans*, including intracranial infections; with *Aspergillus spp.*, including systemic infections in immunocompromised animals; with *Microsporium spp.*; and with *Trichophyton species*. 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.

### **In Vitro Studies**

**The clinical relevance of *in vitro* results obtained with azoles is unknown since MIC (minimal inhibitory concentration) can vary greatly depending on the methods and medium used.** However, in a defined medium the geometric mean MIC of fluconazole for most *Candida* species lies between 0.5 and 1.5 mcg/mL. Fluconazole is apparently less potent against dermatophytes and other filamentous fungi although good *in vivo* activity against these organisms has been demonstrated in animal models (see Table 7).

**Table 7**  
**The mean MIC\* (mcg/mL) and MIC range of fluconazole for various pathogenic fungi in a defined medium\*\***

<i>Strains</i>	Number of Isolates	Fluconazole MIC	Range MIC
<i>Candida albicans</i>	159	0.39	0.1 - 1.56
<i>Candida glabrata</i>	3	1.9	1.56 - 3.12
<i>Candida guilliermondii</i>	3	0.62	0.39 - 0.78
<i>Candida krusei</i>	10	>25	>25
<i>Candida parapsilosis</i>	19	1.0	0.39 - 3.1
<i>Candida pseudotropicalis</i>	6	0.19	0.04 - 0.39
<i>Candida tropicalis</i>	16	1.42	0.19 - 3.12
<i>Cryptococcus neoformans</i>	5	1.25	0.39 - 6.25
<i>Rhodotorula glutinis</i>	1	25	-
<i>Microsporium canis</i>	4	9.4	6.25 - 12.5
<i>Microsporium gypseum</i>	1	50	-
<i>Trichophyton mentagrophytes</i>	21	>100	25 - >100
<i>Trichophyton rubrum</i>	29	39	12.5 - 100
<i>Trichophyton soudanense</i>	2	100	100 - >100
<i>Trichophyton tonsurans</i>	4	42	12.5 - 100
<i>Trichophyton verrucosum</i>	3	37.5	12.5 - 50
<i>Aspergillus flavus</i>	3	>100	>100
<i>Aspergillus fumigatus</i>	7	>100	>100
<i>Aspergillus niger</i>	5	>100	>100
<i>Aspergillus terreus</i>	4	>100	>100

\* Values where 3 or more organisms are used are geometric means.

\*\*Defined tissue culture medium consists of Eagles minimal medium with Earle's salts, yeast carbon base and phosphate buffer, pH 7.5, with or without agar.

## In Vivo Studies

### Systemic Candidosis in Normal Animals

In an acute model in mice or rats infected with *Candida albicans*, untreated animals die within 2 days. After oral treatment with fluconazole at 1, 4 and 24 hours post-infection, the ED<sub>50</sub> at 2 days was 0.08 mg/kg in mice and 0.22 mg/kg in rats. Fluconazole was 20 to 100-fold more potent than ketoconazole in these acute infections. The intravenous ED<sub>50</sub> of fluconazole in mice was 0.06 mg/kg at 2 days, which was comparable to that (0.07 mg/kg) for amphotericin B. However, fluconazole was less active than amphotericin B after 5 days.

In a less acute model, untreated mice die within 7-25 days. After oral therapy once daily for 10 days, the ED<sub>50</sub> values 20 days post-infection were 0.6 mg/kg and >10 mg/kg for fluconazole and ketoconazole respectively. When therapy was extended to 30 days, 90% of mice receiving 2 mg/kg fluconazole but only 50% of those receiving 100 mg/kg ketoconazole survived for 90 days post-infection.

### Systemic Candidosis in Immunosuppressed Mice

Mice made neutropenic with cyclophosphamide are some 10 times more sensitive to an acute *Candida* infection than immune competent animals and untreated controls die within 24 hours. After oral therapy 1, 4, and 24 hours post-infection, the ED<sub>50</sub> values for fluconazole in such animals 2 and 5 days post-infection were 0.39 mg/kg and 0.88 mg/kg, respectively. Corresponding values for ketoconazole were 41.0 mg/kg and >50 mg/kg respectively.

Mice receiving daily dexamethasone are twice as sensitive to a less acute infection than normal animals and untreated controls die within 10 days. Oral therapy for 10 days gave ED<sub>50</sub> values 9 and 15 days post-infection for fluconazole of 0.09 mg/kg and 3.5 mg/kg, while for ketoconazole they were 17 mg/kg and >50 mg/kg respectively. Thus, fluconazole maintains approximately a 50-fold greater potency versus ketoconazole in immunosuppressed animal models of systemic infection.

Mice immunosuppressed with cortisone and meclorothamine (nitrogen mustard) are susceptible to a far lower infectious dose of *C. albicans* than immune normal animals. Fluconazole (at the low doses of 0.1, 0.2, 0.4, or 0.6 mg/kg p.o.) or ketoconazole (6.2, 12.5 or 25 mg/kg p.o.) were administered b.i.d. starting 1 hour post-infection for 2 to 9 days alone or in combination with amphotericin B (1 mg/kg i.p.) once daily for 7 days starting 48 hours post-infection. Untreated animals had a Mean Survival Time (MST) of 5.2 days. Fluconazole alone prolonged survival in a dose-dependent manner up to 0.4 mg/kg p.o. as did ketoconazole from 6.2 to 25 mg/kg p.o. Only 3 of the animals receiving amphotericin B died during the 30 day experiment. Combination of fluconazole (0.4 or 0.6 mg/kg p.o.) or ketoconazole (12.5 or 25 mg/kg p.o.) for 2 to 9 days with amphotericin B further increased survival such that only 2 of the 160 animals used died during the 30 day experiment.

### Cryptococcosis in Normal Mice

Intravenous infection of *C. neoformans* yeasts results in the death of untreated mice within 14 days. Oral therapy with 5 mg/kg fluconazole significantly increased (approximately 20 times) survival rates of these mice as compared to animals given 50 mg/kg of ketoconazole. Animals



given 50 mg/kg fluconazole showed survival rates similar to those receiving 3 mg/kg i.p. of amphotericin B. When cryptococcal yeast cells were injected intracranially, amphotericin B (3 mg/kg i.p.) gave a somewhat better survival rate than fluconazole (5 mg/kg p.o.) although cryptococcal numbers in brain, lungs, and spleen were similar. Ketoconazole at 50 mg/kg p.o. was less effective.

In a chronic pulmonary infection produced by intranasal instillation of  $2 \times 10^5$  yeast cells, fluconazole (10 to 50 mg/kg p.o.) produced a dose-dependent reduction of between approximately  $10^2$  and  $10^4$  in the number of cryptococcal cells per g of lung tissue compared with the lung burden in control animals. In this respect, fluconazole at 50 mg/kg p.o. was considerably more active than 50 mg/kg p.o. of ketoconazole and as effective as 1 mg/kg i.p. amphotericin B.

Intracranial infection of *C. neoformans* causes a slowly progressive infection in immune normal mice. Therapy was with fluconazole (1.25, 2.5, 5.0 or 10.0 mg/kg p.o.) once on the day of infection and then b.i.d. for 9 days alone or in combination with amphotericin B (0.125, 0.175, 0.25, 0.5 or 1.0 mg/kg i.p.) once daily starting on the day of infection. Efficacy was measured by estimating the number of viable *C. neoformans* cells per g of brain tissue 24 hours after the end of therapy. Both fluconazole (1.25 to 10 mg/kg) and amphotericin B (from 0.175 to 1.0 mg/kg) alone produced a dose-dependent decrease in the number of viable *C. neoformans* cells in the brain compared with control animals. Neither compound alone or in combination could completely clear the brain burden of cryptococci and there was no evidence of an interaction, either positive or negative, between these two agents.

#### Systemic Aspergillosis in Normal Mice

Fluconazole (50 mg/kg p.o. b.i.d.) or ketoconazole (50 mg/kg p.o. b.i.d.), were administered either alone or in combination with amphotericin B (2 mg/kg i.p.) given once daily starting 1 hour post-infection. Amphotericin B alone prolonged survival of infected animals compared with either azole alone and untreated controls. Fluconazole alone also prolonged survival compared with ketoconazole alone and untreated controls. Fluconazole given for 9 days or ketoconazole given for 2 or 9 days (both at 50 mg/kg p.o.) in combination with amphotericin B reduced survival compared with animals receiving amphotericin B alone.

#### Systemic Aspergillosis in Immunosuppressed Mice

Mice severely immunocompromised with cortisone and meclorothamine and systemically infected with *Aspergillus fumigatus* died within 6 days. Fluconazole or ketoconazole at 50 mg/kg p.o. b.i.d. for 2 to 9 days failed to increase survival above that of control animals. Amphotericin B (1 mg/kg i.p.) given for 7 days starting 2 days post-infection markedly increased survival over control and azole-treated animals. Those animals receiving either azole plus amphotericin B showed reduced survival compared with those receiving amphotericin B alone.

#### Development of Resistance and Cross-Resistance to Fluconazole

Development of fungal resistance to fluconazole and effects of long-term administration of fluconazole on normal flora have not been systematically investigated.

Significant fungistatic activity of fluconazole was observed against ketoconazole-resistant *Candida albicans* in a neutropenic rabbit model although doses of the order of 80 mg/kg were

required. In another study, however, a strain of *Candida albicans* isolated from a patient with chronic mucocutaneous candidosis who had relapsed during treatment with ketoconazole was not only cross-resistant to all azole antifungals *in vitro* but also in animal models *in vivo*.

High grade azole resistance appears to be cross-reactive *in vivo* against all other imidazole and triazole antifungal drugs.

The clinical correlation of these data has not been precisely established at this time.

## **PHARMACOLOGY**

Fluconazole is a polar bis-triazole antifungal drug. Studies have shown that fluconazole exhibits specificity as an inhibitor of the fungal as opposed to mammalian cytochrome P-450 mediated reactions, including those involved in steroid biosynthesis and drug metabolism. Many of the clinical advantages of fluconazole are a result of its unique pharmacokinetic properties.

### **HUMAN Adults**

#### **Absorption**

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes and do not appear to be affected by gastric pH. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Essentially all of the administered drug reaches systemic circulation; thus, there is no evidence of first-pass metabolism of the drug. In addition, no adjustment in dosage is necessary when changing from p.o. to i.v. or *vice versa*.

Peak plasma concentrations ( $C_{max}$ ) in fasted normal volunteers occur rapidly following oral administration, usually between 1 and 2 hours of dosing with a terminal plasma elimination half-life of approximately 30 hours (range 20 to 50 hours) after oral administration. The long plasma elimination half-life provides the basis for once daily dosing with fluconazole in the treatment of fungal infections.

In fasted normal volunteers, administration of a single oral 400 mg dose of fluconazole leads to a mean  $C_{max}$  of 6.72 mcg/mL (range: 4.12 to 8.08 mcg/mL) and after single oral doses of 50 to 400 mg, fluconazole plasma concentrations and AUC (area under the plasma concentration-time curve) are dose proportional.

In normal volunteers, oral bioavailability as measured by  $C_{max}$  and AUC was not affected by food when fluconazole was administered as a single 50 mg capsule; however  $T_{max}$  was doubled.

Steady-state concentrations are reached within 5 to 10 days following oral doses of 50 to 400 mg given once daily. Administration of a loading dose on the first day of treatment of twice the usual daily dose results in plasma concentrations close to steady state by the second day.

#### **Pharmacokinetics in Children**

In children, the following pharmacokinetic data {mean (% cv)} have been reported (see Table 8).

**Table 8**

Age Studied	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (hour)	C <sub>max</sub> (µg/mL)	Vdss (L/kg)
9 months – 13 years	Single - Oral 2 mg/kg	0.40 (38%) n=14	25.0	2.9 (22%) n=16	—
9 months – 13 years	Single - Oral 8 mg/kg	0.51 (60%) n=15	19.5	9.8 (20%) n=15	—
5 - 15 years	Multiple i.v. 2 mg/kg	0.49 (40%) n=4	17.4	5.5 (25%) n=5	0.722 (36%) n=4
5 - 15 years	Multiple i.v. 4 mg/kg	0.59 (64%) n=5	15.2	11.4 (44%) n=6	0.729 (33%) n=5
5 - 15 years	Multiple i.v. 8 mg/kg	0.66 (31%) n=7	17.6	14.1 (22%) n=8	1.069 (37%) n=7

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 (17%).

In premature newborns (gestation age 26 to 29 weeks), the mean (% cv) clearance within 36 hours of birth was 0.180 mL/min/kg (35%, n=7), which increased with time to a mean of 0.218 mL/min/kg (31%, n=9) 6 days later and 0.333 mL/min/kg (56%, n=4) 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six (6) days later and 46.6 hours 12 days later.

The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients (see Table 9):

**Table 9**

Pediatric Patients	Adults
3 mg/kg	100 mg
6 mg/kg	200 mg
12 mg/kg*	400 mg

\* Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

### Distribution

The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11 to 12%) and is constant over the concentration range tested (0.1 mg/L to 10 mg/L). This degree of protein binding is not clinically meaningful. Following either single- or multiple-oral doses for up to 14 days, fluconazole penetrates into all body tissues and fluids studied (see Table 10). In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations regardless of dose, route, or duration of dosing. In patients with bronchiectasis, sputum concentrations of fluconazole following a single 150 mg oral

dose were equal to plasma concentrations at both 4 and 24 hours post dose. In patients with fungal meningitis, fluconazole concentrations in the CSF (cerebrospinal fluid) are approximately 80% of the corresponding plasma concentrations. Whole blood concentrations of fluconazole indicated that the drug freely enters erythrocytes and maintains a concentration equivalent to that of plasma.

**Table 10**

<b>Tissue or Fluid</b>	<b>Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*</b>
Cerebrospinal fluid <sup>+</sup>	0.5 - 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2

\*Relative to concurrent concentrations in plasma in subjects with normal renal function.

+Independent of degree of meningeal inflammation.

#### Metabolism and Excretion

Fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Following administration of radiolabeled fluconazole, greater than 90% of the radioactivity is excreted in the urine. Approximately 11% of the radioactivity in urine is due to metabolites. An additional 2% of the total radioactivity is excreted in feces.

The pharmacokinetics of fluconazole does not appear to be affected by age alone but are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION may need to be reduced in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

### Pharmacodynamics

The effects of fluconazole on the metabolism of carbohydrates, lipids, adrenal and gonadal hormones were assessed. In normal volunteers, fluconazole administration (doses ranging from 200 to 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations and the adrenocorticotrophic hormone (ACTH)-stimulated cortisol response. In addition, fluconazole appears to have no clinically significant effects on carbohydrate or lipid metabolism in man.

### Animal

**Table 11 illustrates key parameters of fluconazole in the mouse, rat and dog as compared to man.**

**Table 11**

Parameter	Mouse	Rat	Dog	Man
Elimination Half-life (hr)	5.0 (2.6)	4.0	15 (13)	20-50
Plasma Clearance (mL/min/kg)	2.0 (6.2)	2.2	0.62 (0.65)	--(0.28)
Renal Clearance (mL/min/kg)	1.4 (5.0)	1.8	0.30 (0.46)	0.27 (0.26)
Urinary Excretion (% of unchanged drug)	70 (68)	82	63 (72)	80 (75)
Total Urinary Recovery <sup>a</sup> (% of dose)	79 (78)	—	72 (80)	91

Values in parentheses are from intravenous administration; all others are from oral administration.

<sup>a</sup>Total radioactivity.

In all species and man: (1)  $C_{max}$  levels are similar after normalization for different body mass, (2) volume of distribution is about 0.8 L/kg, (3) plasma protein binding is in the range of 11-12% and (4) bioavailability is greater than 80%.

Plasma concentrations of fluconazole generally declined in a monophasic manner with first order kinetics. The elimination half-life ranges from about 2 to 5 hours in the mouse to approximately 30 hours in man (range 20-50 hours). The longer elimination half-life in man is a consequence of low plasma clearance (0.28 mL/min/kg) relative to the normal glomerular filtration rate (1.8 mL/min/kg).

### GENERAL

The general pharmacological properties of fluconazole were investigated in a variety of *in vitro* and *in vivo* tests. The compound was well tolerated in the rat following acute administration of 2.5 and 5.0 mg/kg both orally or intravenously. The normal behavior pattern was not greatly affected and there were no suggestions of an effect on various physiological systems apart from the animals appearing slightly subdued after 5 mg/kg intravenous (i.v.) and showing reduced food intake on the first day following 5 mg/kg orally or intravenously.

In the mouse rotarod test designed to detect sedative and/or skeletal muscle relaxant activity, fluconazole at 5 mg/kg p.o. had no effect 1 hour after administration and produced a slight reduction in performance after 3 hours. It did not affect alcohol sleeping times in mice but significantly prolonged pentobarbital sleeping time. At concentrations up to 100  $\mu$ M, fluconazole did not stimulate intestinal muscle directly or show antimuscarinic or antihistaminic activity on the isolated guinea pig ileum.

Intravenously administered fluconazole at doses up to and including 5 mg/kg was well tolerated by the anesthetized cat. It produced moderate cardiovascular changes which were transient and returned to pretreatment levels within 10 minutes of administration. In the cat, fluconazole did not display sympathomimetic, or ganglion stimulating or blocking activity. Minor alterations in the cardiovascular responses to norepinephrine, isoproterenol, histamine and acetylcholine occurred but were not sufficiently marked or consistent to indicate a direct effect of fluconazole on the receptors for these drugs. Additionally, fluconazole had no anti- 5-hydroxytryptamine activity. Somatic function remained essentially normal and respiration was unchanged.

Fluconazole 5 mg/kg p.o. did not significantly affect the basal gastric acid secretion or motility components of gastrointestinal function in the rat. The drug had no significant effect on renal function as measured by assessing the excretion of fluid and electrolytes in the saline-loaded female rat.

## **TOXICOLOGY**

### **a) Acute Toxicity**

#### **Adult animals**

Fluconazole had extremely low toxicity when administered orally in single doses to male and female mice and rats; no deaths occurred at doses below 1000 mg/kg in either species. The first clinical signs noted were incoordination and decreased activity and respiration at doses greater than 500 mg/kg in mice, while only decreased activity was seen in rats at this 500 mg/kg dose; at higher doses signs included ataxia, prostration, exophthalmia, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex and cyanosis. Some signs appeared from 10 minutes post-dose and most regressed by the second day. The deaths which occurred at doses greater than 1000 mg/kg, were generally within 5 hours post-dose, but occasionally up to 3 days post-dose. Death was sometimes preceded by clonic convulsions. Fluconazole also displayed low toxicity after single intravenous doses. No deaths occurred in male or female mice at 200 mg/kg, in rats at 165 mg/kg or in dogs at 100 mg/kg. Clinical signs, lasting up to 5 to 7 hours, included ataxia, exophthalmia, decreased activity and decreased respiration. Dogs which received single intravenous doses of 100 mg/kg showed only transient clinical signs (ataxia, decreased spontaneous movement and decreased respiration).

#### **Neonatal animals**

Fluconazole was given to 5-day old male and female rats at single doses of 500 or 1000 mg/kg orally or 200 mg/kg intraperitoneally. Mortality occurred 1-3 days after treatment in 4/5 males and females given 1000 mg/kg. Signs of toxicity occurred at oral doses greater than 500 mg/kg

and included decreased activity and respiration, hypothermia and depression of suckling behaviour. At necropsy the liver and/or lungs of these animals were congested.

Fluconazole was given to 20-21 day old male and female beagle dogs as a single oral dose of 300 mg/kg or an intravenous dose of 100 mg/kg. Dogs given fluconazole orally had decreased activity and were ataxic within 20 minutes of dosing. There was a slight increase in BUN and triglyceride concentrations 6 hours after dosing. These dogs had returned to normal within 24 hours of dosing. Dogs given 100 mg/kg intravenously were prostrate, ataxic and had decreased activity immediately after dosing. These signs disappeared in approximately 1 hour. There were slight decreases in RBC parameters during the first 2 days post-dose and a slight increase in triglyceride concentration 6 hours after dosing.

## b) Subacute/Chronic Toxicity

### Adult animals

Subacute and chronic toxicity studies were conducted by the oral and intravenous routes in mice, rats and dogs over one, three, six and twelve months. The dose levels used in the 1-month toxicity studies in mice and dogs (2.5 to 30 mg/kg) revealed target organ toxicity without affecting survival. These doses were maintained for use in the 6 month studies, but reduced slightly for the 12 month study.

In all three species, the liver was found to be the primary target organ for fluconazole toxicity. This was evidenced by an increase in serum aminotransferase concentrations, increases in relative liver weight, and the appearance of liver vacuolation and fatty deposits in the 3 and 6 month studies. These findings were seen more often in males than in females. The 12 month studies in rats and dogs confirmed the results of the 6 month studies. The magnitude of the hepatic changes in all three species was never severe. In addition, in mice treated for 6 months and rats for 12 months, followed by withdrawal of drug, the changes regressed completely within 3 months. In all three species, high doses of fluconazole raised cytochrome P-450 concentrations and caused proliferation of the smooth endoplasmic reticulum. The increased liver weight observed appeared to be due in part to enzyme induction and adaptive hypertrophy.

Two week and six month parenteral studies were also conducted in mice, rats and dogs. In the mouse and rat studies, similar mild liver changes occurred as seen in the oral studies. In the rat, all the changes regressed within 2 months of drug withdrawal.

### Neonatal animals

Fluconazole was given orally to neonatal rats at doses of 10, 30 and 90 mg/kg/day for 18 days from days 4 to 21 postpartum. There was a decrease in body weight gain at 30 and 90 mg/kg. There was a slight increase in relative liver weight in the rats given 90 mg/kg. Microscopically there was centrilobular hepatocytic vacuolation at 90 mg/kg. The vacuolation corresponded to fat deposition.

Fluconazole was given either orally or intraperitoneally daily for 4 weeks to neonatal rats from days 5 through 32 postpartum. The oral doses were 20, 50 and 100 mg/kg/day and the I.P. doses were 10 and 30 mg/kg/day. There was an increase in absolute and relative liver weights in female

rats given oral doses of 50 mg/kg/day, and in males and females given 100 mg/kg/day.

Microscopically, hepatocellular hypertrophy was found in some of the rats given 50 mg/kg/day and in all the rats given 100 mg/kg/day. This was accompanied by fatty vacuolation of hepatocytes in the centrilobular region in some of the rats given 100 mg/kg/day. There were no findings in any of the animals given 10 or 30 mg/kg/day intraperitoneally.

Fluconazole was given to rats intraperitoneally at doses of 2.5, 5 or 25 mg/kg/day for 12 months. Treatment-related findings were observed at the highest dose of 25 mg/kg/day and included: in the males a slight decrease in bodyweight gain, decrease in total cholesterol and an increase in relative liver weights; in both sexes there was a decrease in triglycerides. There were no treatment-related gross necropsy findings. Histopathologic examination was not conducted.

There were no treatment-related findings in the 4-week study in which fluconazole was given at doses of 2.5, 7.5 and 30 mg/kg/day orally to beagle dogs from day 21 or 22 postpartum.

Findings in neonatal animals studied were expected and consistent with those found in adult animals.

**c) Cardiotoxicity**

Administration of fluconazole (30 mg/kg for 14 days; mean plasma concentrations of 39.9 to 71.9 ug/ml) to dogs chronically instrumented to record cardiovascular parameters had no effect on cardiac contractility. However, an increase in blood pressure, left ventricular systolic and end-diastolic pressures and the QTc interval of the ECG was observed when compared to vehicle treated animals. These effects were proportional to drug plasma levels.

**d) Carcinogenicity**

A 24 month study was conducted in mice at 2.5, 5.0 and 10.0 mg/kg. The highest dose was chosen with reference to hepatic changes observed in the six-month study. Mild hepatic fatty deposition was observed in all dose groups. A few cases of centrilobular hypertrophy were also observed in males at 5 and 10 mg/kg. The only tumors seen were those which occurred spontaneously in the strain of mouse used and their incidence was not treatment related.

A 24 month study was also done in rats at 2.5, 5.0 and 10 mg/kg. The target organ was again the liver with centrilobular fatty deposition observed in males at all doses. There was a slight, but statistically significant, increase in the incidence of hepatocellular adenomas in male rats with increasing doses of fluconazole. There were no hepatocellular carcinomas in any group. The incidence of the hepatocellular adenomas was also higher than the historical in-house controls. There was also a decreased incidence of mammary gland fibroadenomas in females and benign adrenal medullary pheochromocytomas in males. Both these decreases were statistically significant.

Fluconazole, when administered to rodents at high dose levels, is known to affect the biochemical balance of male and female hormones. It has been shown to reduce the levels of several steroids, including the ovarian production of 17- $\beta$ -estradiol in female rats, increase placental weights, reduce uterine weights and increase testicular weights in rats in chronic studies. The change in the



pattern of tumors in this chronic study of fluconazole in rats is an expected consequence of such a hormone imbalance.

e) **Mutagenicity**

Ames testing was done with four different strains of Salmonella with and without metabolic activation. Point mutation activity was assessed in the mouse lymphoma L5178Y system with and without metabolic activation. Urine from mice treated orally with fluconazole was also examined for excreted mutagens. Cytogenetic assays *in vivo* were conducted in the mouse bone marrow after single doses up to 600 mg/kg and subacute doses of 80 mg/kg for 5 days. Studies *in vitro* used human lymphocytes with drug concentrations of up to 1000 mcg/mL. Fluconazole revealed no potential mutagenic activity in any of the assays done.

f) **Reproduction and Teratology**

Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies: at 5, 10 and 20 mg/kg, and at 5, 25 and 75 mg/kg respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 9.4 times the maximum recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at the 25 mg/kg dose. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg (approximately 10-40 times the maximum recommended human dose), embryoletality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

General Fertility (Segment I and III) in rats:

Male rats were treated for 80 days prior to and during mating while female rats were treated for 14 days prior to and during mating and through pregnancy and lactation. Both sexes were treated orally with 5, 10 or 20 mg/kg of fluconazole. The treatment was without effect on male or female fertility and labour and did not impair the development, behaviour or fertility of the offspring. The fetuses from the dams sacrificed on day 20 p.i. showed delays in development (an increased incidence of supernumerary ribs at all dose levels and of hydroureters at 20 mg/kg). In the dams allowed to litter, the duration of gestation while remaining within the in-house historical control range, showed a trend towards prolongation in the high dose group. There were no effects on the development, behaviour or fertility of the offspring.

Teratology studies (Segment II) in rats:

The results of teratology studies conducted in 4 different laboratories were remarkably consistent.

In one study, dams were treated orally from day 6 to day 15 of gestation with fluconazole at doses of 5, 10 and 20 mg/kg. At these dose levels, there was no evidence of maternal toxicity, embryotoxicity or teratogenicity.

In a second study, the dams were treated orally from day 7 to 17 of gestation with 5, 25 or 125 mg/kg. Placental weights were increased at 25 and 125 mg/kg and three cases of adactyly (a rare malformation in this strain) were observed at the high dose. There was also an increased incidence of fetal anatomical variants: dilatation of the renal pelvis and bending of the ureter at the high dose, and an increased incidence of supernumerary ribs at both mid and high dose levels.

In a third study, dams were treated orally from day 6 to day 15 of gestation at dose levels of 25, 50, 100 or 250 mg/kg. Placental weights were increased at 50 mg/kg and higher doses. At 100 or 250 mg/kg, there was increased embryomortality and a variety of fetal abnormalities such as: reduced or retarded ossification of sternebral elements, postural defects such as wavy ribs and abnormal cranial ossification. The incidence of supernumerary ribs was increased at all dose levels.

In another study, fluconazole was given orally on days 5-15 of gestation at dose levels of 80, 160 and 320 mg/kg. The vehicle used (Polyethylene Glycol, PEG-400) differed from the vehicle used in earlier studies with fluconazole. It caused maternal effects (an impairment of body weight and food consumption) in all dose groups, with a further drug-related effect being superimposed at the high dose level. Fluconazole, at all dose levels, resulted in an increased number of dead fetuses and resorption sites, and a decreased birth weight of pups. At 320 mg/kg, maternal toxicity was evidenced by decreased food consumption and a reduced increase in body weight. At all dose levels, teratogenicity was evidenced by the presence of multiple visceral and skeletal malformations. Macroglossia, brachygnathia and cleft palate were the main major malformations which showed an increased incidence following dosing with fluconazole. Brachygnathia and cleft palate were increased at doses of 160 and 320 mg/kg while the increase in macroglossia was apparent from 80 mg/kg onwards. Other less commonly observed malformations at 320 mg/kg were those of the eyelids (ablepharia) and ears (bifid ear). A very high incidence of rudimentary 14th ribs, indicating an interference with fetal growth, was observed at all dose levels of fluconazole.

#### Teratology studies (Segment II) in rabbits:

When dams were treated orally from day 6 to 18 of gestation with 5, 10 or 20 mg/kg of fluconazole, the only treatment-related effect was impaired maternal weight gain at the mid and high dose levels. There was no evidence of fetotoxicity or teratogenicity. At dose levels of 25 and 75 mg/kg, maternal body weights were reduced and placental weights were increased at 75 mg/kg. The top dose was toxic for the dams with 6/8 failing to maintain pregnancy to term. There were no effects on the fetuses at 5 or 25 mg/kg and there were too few fetuses at 75 mg/kg to permit a valid assessment of any drug effect.

#### Summary of the teratology studies

Fluconazole did not cause fetal malformations at doses of up to 25 mg/kg in rabbits or 50 mg/kg in rats, doses at which maternal toxicity or hormonal disturbances occurred. The fetal effects at higher dose levels and the effects on parturition at doses of 10 mg/kg and above are consistent with the estrogen-lowering properties demonstrated for fluconazole in rats.

#### Peri- and post-natal study (Segment III) in rats:

Dams were treated intravenously from day 17 of gestation to day 21 post-partum with 5, 20 or 40

mg/kg. This parenteral study confirmed the trend noted in the Segment I study of a delay in the onset of parturition. These disturbances of parturition were reflected in an increase in the number of litters with still-born pups and a slight decrease in pup survival at day 4 in the middle and high dose groups.

g) **Special Toxicity Studies**

- i) Blood compatibility - The formulation of fluconazole dissolved in saline did not cause any hemolysis, flocculation, precipitation or coagulation in human plasma. It did not affect platelet aggregation.
- ii) Ototoxicity in rats - Fluconazole was administered orally to female rats at 100 or 400 mg/kg for 28 days. No ototoxic effect was observed in the Preyer pinna reflex test at 11 different frequencies and no histopathological effect was observed on the cochlea.
- iii) Interaction with AZT - Fluconazole was administered orally to rats at 20 mg/kg twice daily, concurrently with AZT at 40 mg/kg twice daily for 5 days. The combination caused a slight rise in serum sorbitol dehydrogenase as the only treatment-related finding.

h) **Other Studies**

Effects on Estrogen Synthesis

Pregnant rats were treated daily, orally during days 6-15 of gestation with fluconazole (20 or 125 mg/kg) or ketoconazole (10 or 40 mg/kg). Blood samples were taken 3 and 24 hours after the final dose and assayed for 17  $\beta$ -estradiol and progesterone. The results show that both fluconazole and ketoconazole affected steroid metabolism. Fluconazole produced a lower estradiol level at both doses at 3 hours but only at the higher dose at 24 hours. Ketoconazole lowered estradiol levels at both doses at 3 hours only. Fluconazole, on the other hand, lowered progesterone levels only at the higher dose at 24 hours, while ketoconazole lowered it at both time points at both doses.

*In vitro* inhibition of estradiol synthesis was also measured in a broken cell preparation of pregnant rat ovary. The IC<sub>50</sub> for inhibition was 0.55  $\mu$ M for ketoconazole and 8-10  $\mu$ M for fluconazole. Thus, fluconazole is a much weaker inhibitor of estradiol synthesis.

Effects on Host Defence Mechanisms *In Vitro*

Fluconazole at concentrations of 5, 10 and 20 mcg/mL, had little effect (3.4, 5.6 and 1.9% inhibition, respectively) on the destruction of [3H]-uridine-labelled *Candida albicans* blastospores by human polymorphonuclear leukocytes (PMNL) *in vitro*. This suggests that fluconazole has little or no influence on the mechanisms involved in microbial killing by PMNL. In contrast, ketoconazole at 10 and 20 mcg/mL, significantly reduced (20.9 and 55.9%) the release of [3H]-uridine which indicated that it can suppress the destruction of *C. albicans* blastospores by human PMNL *in vitro*.

Similarly, at concentrations of 0.25 to 8 mcg/mL, fluconazole had little effect on the proliferation of concanavalin A and lipopolysaccharide-stimulated mouse spleen lymphocytes as measured by the uptake of [3H]-thymidine. In contrast, ketoconazole at concentrations up to and including 8

µg/mL, significantly reduced the uptake of [3H]-thymidine in the presence of both mitogens.

#### Effects on Key Endocrine Organs

Fluconazole, even at the highest concentration (10 mcg/mL) used, slightly reduced basal and human chorionic gonadotrophin (hCG)-stimulated testosterone secretion by rat Leydig cells *in vitro* (27 and 11% inhibition, respectively) as compared to ketoconazole which markedly reduced (>50%) both secretions.

The release of corticosterone by suspensions of rat adrenal cells incubated *in vitro* with ACTH was not inhibited by fluconazole (25 µM) but was inhibited by ketoconazole (1 µM and above). Similarly, fluconazole at the highest concentration (100 µM) used, produced modest (approximately 23%) inhibition of rat adrenal mitochondrial 11-β hydroxylase activity *in vitro* as compared with the marked, concentration-dependent inhibition produced with ketoconazole (3 and 10 µM).

Comparison of the effects of fluconazole and ketoconazole on the production of estrogens *in vitro* by rat ovarian microsomes showed that fluconazole was approximately 20-fold less potent than ketoconazole as an inhibitor of rat ovarian aromatase (IC<sub>50</sub> values 1.4 µM and 29.6 µM respectively).

Thus, fluconazole appears to be relatively free from effects on mammalian steroid synthesis and to be unlikely to give rise to the endocrine-related side effects in man, or to inhibit adrenal steroid metabolism *in vivo*.

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**CONSUMER INFORMATION****PrTEVA-FLUCONAZOLE  
Fluconazole Tablets  
50 mg and 100 mg****PrFLUCONAZOLE INJECTION  
Solution for Intravenous Infusion  
2 mg/mL  
(100 mL vial; 100 mL and 200 mL Cryovac bags)**

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-FLUCONAZOLE tablets and FLUCONAZOLE INJECTION. Contact your doctor, pharmacist, or hospital (clinic) if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) is one of a group of medicines called antifungals.

TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION are prescribed by your doctor and are used to treat infections caused by fungi including yeasts and may also be used to stop you from getting a fungal infection. The most common cause of fungal infection is a yeast called *Candida*.

**What it does:**

TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION selectively interferes with the normal sterol production in fungi and helps to stop fungal growth.

**When it should not be used:**

Do not take TEVA-FLUCONAZOLE or FLUCONAZOLE INJECTION if you have ever had an allergic reaction to:

- any of the ingredients of TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (see What the important nonmedicinal ingredients are)
- other medicines you have taken to treat a fungal infection.

The symptoms may include itching, reddening of the skin or difficulty in breathing.

Do not take TEVA-FLUCONAZOLE or FLUCONAZOLE INJECTION if you are taking any of the following drugs:

- Cisapride\* (used as a gastrointestinal motility agent),
- Terfenadine\* or astemizole\* (antihistamines for allergies),
- Erythromycin (an antibiotic for treating infections),
- Pimozide (for treating schizophrenia) and
- Quinidine (used for irregular heartbeats).

\* not marketed in Canada

**What the medicinal ingredient is:**

fluconazole

**What the important non-medicinal ingredients are:**

TEVA-FLUCONAZOLE tablets contain the following non-medicinal ingredients: dibasic calcium phosphate anhydrous, croscarmellose sodium, microcrystalline cellulose, FD & C Red #40 Aluminum Lakes (alumina hydrate base), povidone, colloidal silicon dioxide, and magnesium stearate.

FLUCONAZOLE INJECTION contains the following non-medicinal ingredients: sodium chloride (isotonicity) and Water for Injection.

**What dosage forms it comes in:**

TEVA-FLUCONAZOLE tablets:

- 50 mg: Bottles of 100.
- 100 mg: Bottles of 50.

FLUCONAZOLE INJECTION sterile aqueous solution for infusion:

- (2 mg / mL): 100 mL vial
- (2 mg / mL): 100 mL and 200 mL Cryovac bags

**WARNINGS AND PRECAUTIONS**

**BEFORE you use TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) talk to your doctor or pharmacist if you:**

- **have liver or kidney problems**
- **are allergic to any other medicines including those used to treat yeast and other fungal infections**
- **have abnormal levels of potassium, calcium or magnesium in your blood**
- are breast-feeding or planning to breast-feed. Fluconazole is excreted in human breast milk. Breast-feeding is not recommended.
- have heart disease such as heart conditions, blood disorders or any other medical conditions.
- are driving and using machines. It should be taken into account that occasionally dizziness or seizures may occur.
- are taking or have taken any other medicines, including medicines obtained without a prescription

**Use in Children**

- Your doctor will decide whether this medication is suitable for your child.

**Use in Pregnancy**

- TEVA-FLUCONAZOLE or FLUCONAZOLE INJECTION may cause harm to your unborn baby.
- If you are pregnant or planning to become pregnant, talk to your doctor.
- TEVA-FLUCONAZOLE or FLUCONAZOLE INJECTION should not be used in pregnancy except in severe or life-threatening infection.
- Your doctor will decide if TEVA-FLUCONAZOLE or FLUCONAZOLE INJECTION should be used in your

situation.

If you are a woman of child-bearing potential then:

- Avoid becoming pregnant during treatment
- Use effective contraception during treatment and for 1 week after treatment
- Tell your doctor if you become pregnant during treatment.

### INTERACTIONS WITH THIS MEDICATION

**Drugs that may interact with TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) include:**

- Alfentanil, fentanyl or methadone (used to treat pain)
- Amitriptyline, nortriptyline (used to treat migraine and other conditions)
- Amphotericin B and Voriconazole (used to treat fungal infections)
- Benzodiazepines such as midazolam, triazolam, or similar medicines (used to help you sleep or for anxiety)
- Calcium channel blockers or losartan (for lowering blood pressure)
- Carbamazepine or phenytoin (used to control epilepsy)
- Celecoxib (used to treat some types of arthritis and certain other types of pain)
- Cimetidine (for heartburn and peptic ulcers)
- Coumarin-Type Anticoagulants (used to thin the blood to prevent blood clots)
- Cyclophosphamide, or vinca alkaloids (for treating some forms of cancer)
- Cyclosporine, sirolimus or tacrolimus (to prevent transplant rejection)
- Halofantrine (to treat malaria)
- HMG-CoA reductase inhibitors (statins) (for lowering cholesterol)
- Medicines for treating infections (antibiotics) such as azithromycin, erythromycin, rifampin or rifabutin
- Non-steroidal anti-inflammatory drugs (such as acetylsalicylic acid and ibuprofen) that are used to treat pain and fever
- Oral Contraceptives
- Prednisone (used to treat many types of inflammatory and allergic conditions)
- Saquinavir or zidovudine, also known as AZT (used in HIV-infected patients)
- Sulfonylureas and other Oral Hypoglycemics (medicines for diabetes)
- Theophylline (used to control asthma)
- Tofacitinib (used to treat rheumatoid arthritis)
- Vitamin A (as a trans-retinoid acid used to treat acne)
- Water tablets (diuretics), such as hydrochlorothiazide, (used to treat fluid retention and high blood pressure)

### PROPER USE OF THIS MEDICATION

### USUAL DOSE:

Take Fluconazole only as directed by your doctor.

### OVERDOSE:

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

### MISSED DOSE:

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double dose.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, **TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole)** may cause some side effects.

The most common side effects are:

- Headache,
- Skin rash,
- Abdominal pain,
- Diarrhea,
- Nausea and vomiting.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<b>Exfoliative skin disorders:</b> Severe skin reactions, such as a rash that causes blistering, itching all over the body, reddening of the skin or itchy red spots, swelling of eyelids, face or lips, peeling or lost skin		✓	
<b>Hepatic necrosis</b> (death of liver cells which may cause abdominal pain and dark urine, fever, light-colored stool, and jaundice (a yellow appearance to the skin and white portion of the eyes))		✓	
<b>Heart conditions:</b> Unstable or irregular heartbeat (e.g. QT prolongation, torsade de pointes)		✓	

Allergic Reaction with symptom such as swelling of the face, throat, mouth, extremities, difficulty in breathing, rash or itching			✓
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***This is not a complete list of side effects. For any unexpected effects while taking TEVA-FLUCONAZOLE and FLUCONAZOLE INJECTION, contact your doctor or pharmacist immediately.***

**HOW TO STORE IT**

TEVA-FLUCONAZOLE tablet: Store bottles between 15°C- 30°C. Keep out of sight and reach of children.  
 FLUCONAZOLE INJECTION: Store vials between 15°C- 30°C. Store bags between 5°C - 25°C. Do not freeze.

**REPORTING SIDE EFFECTS**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

**If you want more information about TEVA-FLUCONAZOLE:**

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://www.hc-sc.gc.ca/>); the manufacturer’s website <http://www.tevacanada.com>; or by calling 1-800-268-4127 ext. 3; or email [druginfo@tevacanada.com](mailto:druginfo@tevacanada.com).

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