PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FLUCONAZOLE 150

Fluconazole Capsule

Capsule, 150 mg

House Standard

Oral Antifungal Agent

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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June 02, 2010

Date of Revision:
MAR 09, 2023

Submission Control Number: 271182

RECENT MAJOR LABEL CHANGES

9 DRUG INTERACTIONS	03/2023
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

FLUCONAZOLE 150 (fluconazole) is indicated for the single-dose treatment of vaginal candidiasis (yeast infections due to *Candida*) and is clinically proven to cure most vaginal yeast infections.

1.1 Pediatrics

Pediatrics (>12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of fluconazole in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see **7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics**).

2 CONTRAINDICATIONS

- **FLUCONAZOLE 150** is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of the excipients used. See the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the product monograph for a complete listing of excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used by individuals having hypersensitivity to other azoles when using fluconazole.

- Co-administration of terfenadine* is contraindicated in patients receiving fluconazole at multiple doses of 400 mg/day or higher based upon results of a multiple-dose interaction study (see **9 DRUG INTERACTIONS**).

- Co-administration of astemizole* is contraindicated in patients receiving fluconazole (see **9 DRUG INTERACTIONS**).

- Co-administration of cisapride* is contraindicated in patients receiving fluconazole (see **9 DRUG INTERACTIONS**).

- Co-administration of drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as amiodarone, erythromycin, pimozide and quinidine are contraindicated in patients receiving fluconazole (see **9 DRUG INTERACTIONS**).

*not marketed in Canada

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage of **FLUCONAZOLE 150** for vaginal candidiasis is 150 mg as a single oral dose.
- There is no need to adjust single-dose therapy for vaginal candidiasis because of impaired renal function.

5 OVERDOSAGE

Symptoms: There have been reports of overdosage with fluconazole and in one reported case, a 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to the hospital, and his condition resolved within 48 hours.

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 3- 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule, 150 mg	Colloidal silicon dioxide, croscarmellose sodium, gelatin, lactose monohydrate, microcrystalline cellulose, pharmaceutical ink, stearic acid, talc and titanium dioxide.

FLUCONAZOLE 150 capsules are available as a hard, white, opaque, gelatin capsule, imprinted with APO F150.

Each capsule contains 150 mg of fluconazole. Supplied as a unit dose blister pack of 1 capsule.

7 WARNINGS AND PRECAUTIONS

General

FLUCONAZOLE 150 is indicated for single dose only. Some (not all) adverse experiences have been reported in patients following exposure to multiple doses of fluconazole.

The convenience of the single oral dose fluconazole regimen for the treatment of vaginal yeast infections **should be weighed against the acceptability of a higher incidence of drug related adverse events** with oral fluconazole (26%) versus intravaginal agents (16%) in comparative clinical studies where no difference in efficacy was demonstrated (see **8 ADVERSE REACTIONS**).

Fluconazole administered in combination with ethinyl estradiol- and levonorgestrel-containing oral contraceptives produced an overall mean increase in ethinyl estradiol and levonorgestrel levels; however, in some patients there were decreases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels, respectively (See **9 DRUG INTERACTIONS**). The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment may be the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown.

Cardiovascular

QT Prolongation:

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and Torsade de Pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions (see **9 DRUG INTERACTIONS** and **8 ADVERSE EFFECTS**).

Endocrine and Metabolism

Adrenal insufficiency has been reported in patients receiving other azoles (e.g., ketoconazole). Reversible cases of adrenal insufficiency were reported in patients receiving fluconazole or when fluconazole was discontinued (see **9 DRUG INTERACTIONS**).

Hepatic/Biliary/Pancreatic

In the treatment of systemic infections, multiple doses of fluconazole have 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.

Immune
In rare cases, anaphylaxis and angioedema have been reported in patients using fluconazole.

Sensitivity/Resistance
Candidiasis: Studies have shown an increasing prevalence of infections with Candida species other than C. albicans. These are often resistant (e.g., C. krusei and C. auris) or show reduced susceptibility to fluconazole (C. glabrata). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various Candida species to fluconazole (see 15 MICROBIOLOGY).

Skin
In very rare cases, during the treatment of systemic and vaginal infections, patients have developed exfoliative skin disorders (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Single-dose oral fluconazole 150 mg does not appear to increase the risk of congenital anomalies. There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high dose (400 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. Fluconazole should not be used in pregnant women except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus.

Effective contraceptive measures should be considered in women of child-bearing potential and should continue for approximately 1 week (5 to 6 half-lives) after the dose.

Observational studies have suggested an increased risk of spontaneous abortion or birth defects in women treated with fluconazole during the first trimester.

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 9.4x 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 to 40x the maximum recommended human dose) embryolethality 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.

7.1.2 Breast-feeding

Fluconazole is secreted in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended (see **10.3 Pharmacokinetics**).

7.1.3 Pediatrics

FLUCONAZOLE 150 should not be used by girls less than 12 years of age unless advised by a physician.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In patients with vaginal candidiasis treated with fluconazole (150 mg) as a single oral dose, the adverse events documented in two controlled North American trials were as follows:

	Percent of Patients with Side Effects	
	Fluconazole (n = 448)	Intravaginal Products (n = 422)
Drug Related Side Effects	26.1	15.9
Nausea	6.7	0.7
Abdominal Pain	5.6	1.7
Diarrhea	2.7	0.5
Dyspepsia	1.3	0.2
Headache	12.9	6.6

	Percent of Patients with Side Effects	
	Fluconazole (n = 448)	Intravaginal Products (n = 422)
Application Site Reactions	0.0	4.5
Dizziness	1.3	0.0
Taste Perversion	1.3	0.0
Most of the reported side effects were mild to moderate in severity.		

8.3 Less Common Clinical Trial Adverse Reactions

Occasional allergic reactions including pruritus and urticaria were reported.

8.5 Post-Market Adverse Reactions

In marketing experience of single-dose fluconazole, rare cases of anaphylactic reaction and angioedema have been reported.

In addition, the following adverse experiences have been reported in patients under conditions (e.g. open trials, marketing experience fluconazole) where a causal relationship is uncertain or in patients treated with multiple doses of fluconazole:

Cardiovascular: QT prolongation, Torsade de Pointes (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular, QT Prolongation**).

Central and Peripheral Nervous System: seizures.

Dermatologic: alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis (see **7 WARNINGS AND PRECAUTIONS**). Drug reactions with eosinophilia and systemic symptoms (DRESS); causal relationship uncertain. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see **7 WARNINGS AND PRECAUTIONS**).

Gastrointestinal: vomiting.

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

Immunologic: face edema.

Body as a Whole: urticaria

Liver/Biliary: hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional: hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

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

ABROCITINIB
Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If coadministered with fluconazole, adjust the dose of abrocitinib as instructed in abrocitinib prescribing information.

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 concomitant benzodiazepine therapy, such as midazolam or triazolam, is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage.

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 ± SD decrease in fluconazole AUC of 13% ± 11% (range: -3.4 to -31%) and C_{max} decreased 19% ± 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.

COUMARIN-TYPE ANTICOAGULANTS
In a clinical trial, 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 ± SD increase in the prothrombin time response (area under the prothrombin time-time curve) of 7% ± 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.

During the 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.

Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type or indanedione anticoagulants. Dose adjustment of these anticoagulants may be necessary.

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 ± SD increase in AUC was 92% ± 43% (range: 18 to 147%). The C_{max} increased 60% ± 48% range (range: -5 to 133%). The C_{min} increased 157% ± 96% (range: 33 to 360%). The apparent oral clearance decreased 45% ± 15% (range: -15 to -60%). Fluconazole administered at 100 mg daily dose does not affect cyclosporine pharmacokinetic levels in patients with bone marrow transplants. Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment.

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.

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 **2 CONTRAINDICATIONS**).

Cisapride*: There have been reports of cardiac events including Torsade de Pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Co-administration of cisapride is contraindicated in patients receiving fluconazole (see **2 CONTRAINDICATIONS**).

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. Fluconazole 200 mg was administered daily from days 9 through 15. Fluconazole did not affect terfenadine plasma concentrations. Terfenadine acid metabolite AUC increased 36% ± 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. However, another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg/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 **2 CONTRAINDICATIONS**). Patients should be carefully monitored if they are being concurrently prescribed fluconazole at multiple doses lower than 400 mg/day with terfenadine.

*not marketed in Canada

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 **2 CONTRAINDICATIONS**).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of Torsades de Pointes. Coadministration of fluconazole and quinidine is contraindicated (see **2 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 **2 CONTRAINDICATIONS).**

Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of fluconazole and amiodarone is necessary, notably with high-dose fluconazole (800 mg) (see **2 CONTRAINDICATIONS**).

Lemborexant: Concomitant administration of fluconazole increased lemborexant C_{max} and AUC by approximately 1.6- and 4.2-fold, respectively which is expected to increase risk of adverse reactions, such as somnolence. Avoid concomitant use of lemborexant.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases (dose-dependent) when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolized through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). 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. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.

HYDROCHLOROTHIAZIDE

Concomitant oral administration of 100 mg fluconazole and 50 mg hydro-chlorothiazide 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 ± SD increase in fluconazole AUC and C_{max} of 45% ± 31% (range: 19 to 114%) and 43% ± 31% (range: 19 to 122%), respectively. These changes are attributed to a mean ± SD reduction in renal clearance of 30% ± 12% (range -10 to -50%).

IBRUTINIB

Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib as instructed in ibrutinib Product Monograph and provide close clinical monitoring.

IVACAFTOR (alone or combined with drugs in the same therapeutic class) Coadministration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

LURASIDONE Moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.

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 fluconazole. The mean increase in ethinyl estradiol AUC was 6% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

Twenty-five normal females received daily doses of both 200 mg fluconazole 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.

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.

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

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 ± SD increase in AUC of 49% ± 13% (range: 27 to 73%) and an increase in C_{max} of 19% ± 23% (range: -11 to 79%).

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 ± SD increase in AUC of 44% ± 29% (range: -13 to 115%) and C_{max} increased 19% ± 19% (range: -23 to 62%). Five subjects required oral glucose following the ingestion of glyburide after 7 days of fluconazole administration.

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.

PHENYTOIN

Fluconazole increases the plasma concentrations of 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. The mean ± SD increase in phenytoin AUC was 88% ± 68% (range: 16 to 247%). The absolute magnitude of this interaction is unknown because of the intrinsically non-linear disposition of phenytoin.

PREDNISONE

There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a 3-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. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered.

RIFAMPIN

Administration of a single oral 200 mg dose of fluconazole after 15 days of rifampin administered as 600 mg daily in 8 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 ± SD reduction in fluconazole AUC of 23% ± 9% (range: -13 to -42%). Apparent oral clearance of fluconazole increased 32% ± 17% (range: 16 to 72%). Fluconazole half-life decreased from 33.4 ± 4.4 hours to 26.8 ± 3.9 hours.

Rifampin enhances the metabolism of concurrently administered fluconazole.

TACROLIMUS

There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were coadministered.

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 ± SD theophylline AUC increased 21% ± 16% (range: -5 to 48%). The C_{max} increased 13% ± 17% (range: -13 to 40%). Theophylline clearance decreased 16% ± 11% (range: -32 to 5%). The half-life of theophylline increased from 6.6 ± 1.7 hours to 7.9 ± 1.5 hours.

TOLVAPTAN

Exposure to tolvaptan is significantly increased (200% in AUC; 80% in C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse effects particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced and the patient managed cautiously.

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 ± SD increase in AUC was 20% ± 32% (range: -27 to 104%). The metabolite, GZDV, to parent drug ratio significantly decreased after the administration of fluconazole, from 7.6 ± 3.6 to 5.7 ± 2.2.

Drugs exhibiting no significant pharmacokinetic interactions with fluconazole:

ANTACIDS
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.

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

9.5 Drug-Food Interactions

Interactions with foods have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14-α-demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14- β -methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14-alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14-alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole 50 mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on adrenocorticotropic hormone (ACTH) stimulated response in healthy male volunteers.

Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Pharmacokinetic/pharmacodynamic relationship

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

10.2 Pharmacodynamics

The effects of fluconazole on the metabolism of carbohydrates, lipids, adrenal and gonadal hormones were assessed. In normal volunteers, fluconazole administration at 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 adrenocorticotropic hormone (ACTH) stimulated cortisol response. In addition, fluconazole appears to have no clinically significant effects on carbohydrate or lipid metabolism in man.

10.3 Pharmacokinetics

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.

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 behaviour 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 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 mcM, 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 anaesthetized 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.

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 150 mg dose of fluconazole produced a mean C_{max} of 2.70 mcg/mL (range: 1.91 to 3.70 mcg/mL).

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.

A pharmacokinetic study in 10 lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose.

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.

A single oral 150 mg dose of fluconazole administered to 27 patients penetrated into vaginal tissue, resulting in tissue: plasma ratios ranging from 0.94 to 1.14 over the first 48 hours following dosing.

A single oral 150 mg dose of fluconazole administered to 14 patients penetrated into vaginal fluid, resulting in fluid: plasma ratios ranging from 0.36 to 0.71 over the first 72 hours following dosing.

Metabolism and Elimination: Fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Following administration of radiolabelled 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 do 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. There is no need to adjust single-dose therapy for vaginal candidiasis because of impaired renal function.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30 °C).

12 SPECIAL HANDLING INSTRUCTIONS

This information is not available for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

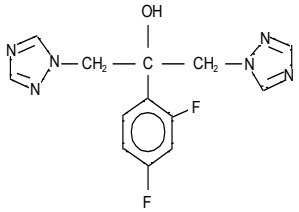
Drug Substance

Proper name: Fluconazole

Chemical name:
1) 1*H*-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α -(1*H*-1,2,4-triazol-1-ylmethyl)-;
2) 2,4-Difluoro-α ,α -bis(1*H*-1,2,4-triazol-1-ylmethyl) benzyl alcohol

Molecular formula and molecular mass: $C_{13}H_{12}F_2N_6O$; 306.28 g/mol

Structural formula:



Physicochemical properties: Fluconazole is a white crystalline solid, freely soluble in methanol, soluble in acetone, sparingly soluble in aqueous 0.1M hydrochloric acid and ethanol, slightly soluble in water and saline and very slightly soluble in hexane.

Fluconazole is a very weak base with a pKa of 1.76 at 24°C and as a consequence will be essentially non-protonated at pH values above 3.5. m.p. = 140.3°C. The partition coefficient Log P = +0.5.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The following studies assessed fluconazole 150 mg single-dose for the treatment and cure of vaginal candidiasis. A total of 13 studies are presented below.

Study Demographics and Trial Design

Study Ref.	Trial Design	Drug and Dose	Study Subjects	Age	No. of Females
Adetoro 1990	RD, O, C	Fluconazole 150 mg po sd	Females with VC	15-39 years	23
Andersen et al. 1989	RD, C, MC	Fluconazole 150 mg po sd	Females with VC	32.1 years	188
Mendling et al. 2004	RD, SB, PL	Fluconazole 150 mg po sd	Females with VC	Unk	154
Mikamo et al 1995	O, C	Fluconazole 150 mg po sd	Females with VC	18-54 years	50
Mikamo et al. 1998	O, C	Fluconazole 150 mg po sd	Females with VC	17-55 years	50
Multicentre Study Group 1988	O	Fluconazole 150 mg po sd	Females with VC	17-67 years	180
O-Prasertsawat & Bourlert 1995	RD, SB	Fluconazole 150 mg po sd	Females with VC	26-43 years	53
Phillips et al. 1990	O, MC	Fluconazole 150 mg po sd	Females with VC	17-65 years	1017
Sobel et al. 1995	RD, SB, MC, C	Fluconazole 150 mg po sd	Females with VC	18-63 years	218
Timonen 1992	RD, O, C	Fluconazole 150 mg po sd	Females with VC	18-54 years	54
van Heusden et al. 1990	RD, DB, DD, PL	Fluconazole 150 mg po sd	Females with VC	18-60 years	43
van Heusden et al. 1994	RD, MC, C	Fluconazole 150 mg po sd	Females with VC	18-65 years	243
Wooley & Higgins 1995	RD, C	Fluconazole 150 mg po sd	Females with VC	27.3 years	72

RD: randomized, O: open, C: comparative, MC: Multicentre, SB: single-blind, PL: parallel, DB: double blind, DD: double-dummy, po: oral, sd: single-dose, VC: vaginal candidiasis, Unk: unknown

14.2 Study Results

Reference	Primary Endpoints	Associated value for fluconazole 150 mg
Adetoro 1990	CC & MC 8 days CC & MC 32 days	87% 87%
Andersen et al. 1989	CC 5 - 16 days CC 27 - 62 days MC 5 - 16 days MC 27 - 62 days	99% 93% 85% 72%
Mendling et al. 2004	MC 14 days MC & CC 14 days	76.0% 59.1%
Mikamo et al 1995	CC 5 - 15 days CC 30 - 60 days MC 5 - 15 days MC 30 - 60 days	80% 76% 76% 70%
Mikamo et al. 1998	CC 5 - 15 days CC 30 - 60 days MC 5 - 15 days MC 30 - 60 days	80% 76% 76% 70%
Multicentre Study Group 1988	CC 5 - 16 days CC 27 - 62 days MC 5 - 16 days MC 27 - 62 days	97% 88% 94% 73%
O-Prasertsawat & Bourlert 1995	CC 7 days CC 28 days MC 7 days MC 28 days	88.7% 69.8% 79.2% 60.4%
Phillips et al. 1990	CC	94.7%
Sobel et al. 1995	CC 14 days CC 35 days MC 14 days MC 35 days	94% 75% 77% 65%
Timonen 1992	CC 7 days MC 7 days MC 30 days	100% 83.3% 72.2%
van Heusden et al. 1990	CC 6 - 10 days CC 22 - 44 days MC 6 - 10 days MC 22 - 44 days	81% 86% 98% 74%
van Heusden et al. 1994	MC 7 days MC 28 days	82% 75%

Reference	Primary Endpoints	Associated value for fluconazole 150 mg
Wooley & Higgins 1995	CC 7 - 10 days MC 7 - 10 days	62% 83%

CC: clinical cure, MC: mycological cure

14.3 Comparative Bioavailability Studies:

A standard, randomized, two-way crossover, single-dose bioavailability study was conducted in twenty (20) healthy, adult, male volunteers to evaluate the relative bioavailability of single oral dose (1 x 150 mg) of FLUCONAZOLE 150 manufactured by Apotex Inc. and Diflucan® 150 Capsule manufactured by Pfizer Canada Inc.

The mean pharmacokinetic parameters of the 17 subjects completing the study are listed in the following table:

Fluconazole (1 x 150 mg) From measured data **uncorrected potency** Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Fluconazole 150 (Apotex Inc.)**	**Diflucan 150® † (Pfizer Canada)**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_{0-72h} (mcg·hr/mL)	87.2 89.9 (20.4)	89.6 92.3 (20.8)	97.3	94.1 - 101
AUC_{I} (mcg·hr/mL)	141.9 147.3 (21.5)	140.8 144.8 (21.8)	100.8	90.6 - 112
C_{max} (mcg/mL)	2.26 2.29 (19.1)	2.76 2.76 (15.4)	81.8	75.5 – 88.8
T_{max} (h)*	5.33 (60.4)	1.67 (45.1)		
$t_{1/2}$ (h)*	44.6 (27.4)	42.1 (21.8)		

* Arithmetic means only (CV%).

† Diflucan 150® is manufactured by Pfizer Canada Inc. and was purchased in Canada.

15 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 *Microsporum spp.*; and with *Trichophyton spp*. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitidis*; with *Coccidioides immitis*; including intracranial infection; and with *Histoplasma capsulatum* in normal and immunosuppressed animals.

***In Vitro* Studies**

In vitro, fluconazole displays antifungal activity against clinically common *Candida* species (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* is intrinsically resistant to fluconazole. The MICs and EUCAST epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans*. The recently emerging species *C. auris* tends to be relatively resistant to fluconazole.

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

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 below)

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

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

Vaginal Candidosis in Predisposed Mice and Rats:
A vaginal *Candida albicans* infection, induced in mice or ovariectomized rats predisposed with estradiol benzoate, was treated orally with a single dose immediately post-infection

(prophylactic) or once daily for 3 days starting 72 h. post-infection (therapeutic). Efficacy was measured as percentage cure compared with untreated controls. In both models in mice or in rats, fluconazole (CD_{50}'s 2.7 and 4.4 mg/kg, respectively, in mice and 2.9 and 2.1 mg/kg, respectively, in rats) was at least 5 to 10 times more effective than ketoconazole (CD_{50}'s 32 and >50 mg/kg, respectively, in mice and 32 and 12.5 mg/kg, respectively, in rats) in this local infection.

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.

Mechanisms of resistance
In usually susceptible species of *Candida*, the most commonly encountered mechanism of resistance involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Point mutations in the gene (*ERG11*) encoding for the target enzyme lead to an altered target with decreased affinity for azoles. Overexpression of *ERG11* results in the production of high concentrations of the target enzyme, creating the need for higher intracellular drug concentrations to inhibit all of the enzyme molecules in the cell.

The second major mechanism of drug resistance involves active efflux of fluconazole out of the cell through the activation of two types of multidrug efflux transporters; the major facilitators (encoded by *MDR* genes) and those of the ATP-binding cassette superfamily (encoded by *CDR* genes). Upregulation of the *MDR* gene leads to fluconazole resistance, whereas, upregulation of *CDR* genes may lead to resistance to multiple azoles.

Resistance in *Candida glabrata* usually includes upregulation of *CDR* genes resulting in resistance to multiple azoles.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity: 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).

Subacute/Chronic Toxicity: 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 transaminase 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.

Cardiotoxicity: Administration of fluconazole (30 mg/kg for 14 days; mean plasma concentrations of 39.9 to 71.9 µg/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.

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 tumours 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 phaeochromocytomas 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-β-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 tumours in this chronic study of fluconazole in rats is an expected consequence of such a hormone imbalance.

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.

Reproduction and Developmental Toxicology:

General Fertility (Segments 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 pregnancy and lactation. Both sexes were treated orally with 5 mg/kg, 10 mg/kg, 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 foetuses 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 foetal 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 mild 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 embryo mortality and a variety of foetal 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 higher dose level. Fluconazole, at all dose levels, resulted in an increased number of dead foetuses and resorption sites and a decreased birthweight 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 foetal 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 foetuses at 5 or 25 mg/kg and there were too few foetuses at 75 mg/kg to permit a valid assessment of any drug effect.

Summary of the teratology studies:
Fluconazole did not cause foetal 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 foetal 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.

Special Toxicology:

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.

Other Studies:

Effects on Estrogen Synthesis:
Pregnant rats were treated daily, orally during days 6 to 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-β-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_{50} for inhibition was 0.55 mcM for ketoconazole and 8 to 10 mcM 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 [^{3}H]-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 [^{3}H]-uridine which indicated that it can suppress the destruction of *Candida 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 [^{3}H]-thymidine. In contrast, ketoconazole at concentrations up to and including 8 mcg/mL, significantly reduced the uptake of [^{3}H]-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 mcM) but was inhibited by ketoconazole (1 mcM and above). Similarly, fluconazole at the highest concentration (100 mcM) 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 mcM).

Comparison of the effects of fluconazole and ketoconazole on the production of estrogen *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_{50} values 1.4 mcM and 29.6 mcM 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*.

17 SUPPORTING PRODUCT MONOGRAPHS

1. DIFLUCAN ONE, Fluconazole Capsule, 150 mg, submission control 268032, Product Monograph, Pfizer Product Inc. (JAN 12, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

FLUCONAZOLE 150

Fluconazole Capsule
Read this carefully before you start taking **FLUCONAZOLE 150** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **FLUCONAZOLE 150**.

What is FLUCONAZOLE 150 used for?

FLUCONAZOLE 150 is indicated for the treatment of vaginal yeast (fungal) infections. It can be taken anytime, anywhere to relieve itching, burning and discharge associated with vaginal yeast infections. **FLUCONAZOLE 150** is a clinically proven, effective single-dose cure for most vaginal yeast infections that starts to work in 1 day.

What is a Yeast Infection?
A "yeast infection" may occur any time there is an overgrowth of yeast organisms in the vagina. The vagina normally has bacteria and yeast organisms present. Under some conditions, the number of yeast organisms rises, irritating the tissues of the vagina and vaginal opening.

Conditions that make this more likely to occur:
- illness
- use of antibiotics
- changes in hormone levels
- pregnancy
- use of oral contraceptive pills
- just before a woman's period
- diabetes
- hot humid weather
- continuous use of panty liners
- tight, non-breathing clothing
- nylon underwear, pantyhose, wet bathing suits or damp workout wear
- perfumed soaps, bubble baths or douching may cause vaginal irritation and upset the normal balance

Refrain from vaginal intercourse when you have a yeast infection to avoid infecting your partner and to minimize additional discomfort. If your partner has any genital itching, redness or discomfort, they should talk to their doctor and mention that you are treating a yeast infection.

When a "yeast infection" occurs, the body responds with:

- an increase in vaginal secretions
- secretions are generally thick and sticky (cheesy or curd-like, similar to cottage cheese), but odourless
- secretions that are irritating to the tissues of the vaginal area
- itching, redness, and swelling of the vaginal area
- red spots or sores may develop, especially if the area has been scratched
- soreness in the vagina
- pain during sexual relations is common.

How does FLUCONAZOLE 150 work?

FLUCONAZOLE 150 is an antifungal medication. The active ingredient fluconazole works by stopping the growth of the fungi that cause vaginal yeast infections.

What are the ingredients in FLUCONAZOLE 150?

Medicinal ingredient: Fluconazole

Non-medicinal ingredients: Colloidal silicon dioxide, croscarmellose sodium, gelatin, lactose monohydrate, microcrystalline cellulose, pharmaceutical ink, stearic acid, talc and titanium dioxide.

FLUCONAZOLE 150 comes in the following dosage forms:

Capsule, 150 mg

Do not use FLUCONAZOLE 150 if:

- you are allergic to fluconazole, related azoles (e.g. clotrimazole / miconazole) or other ingredients in the product (see **What are the ingredients in FLUCONAZOLE 150?**)
- you are taking allergy drugs (e.g. astemizole* / terfenadine*)
- you are taking cisapride*, quinidine, erythromycin, pimozide or amiodarone

*not marketed in Canada

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FLUCONAZOLE 150. Talk about any health conditions or problems you may have, including if:

- you are having your first yeast infection
- you have frequent vaginal infections
- you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often
- you have heart disease
- using in children less than 12 years old

Other warnings you should know about:

Yeast infections do not cause:
- Fever
- Chills
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Pain upon urination
- Unexplained pain in your lower back or either shoulder
- Foul-smelling discharge

Consult your doctor immediately if you have these symptoms, as they could be signs of a more serious condition.

Pregnancy and Breastfeeding:
- You should not use **FLUCONAZOLE 150** if you are pregnant or trying to become pregnant.
- You should not use **FLUCONAZOLE 150** if you are breastfeeding.

There have been reports of spontaneous abortion of the foetus or birth defects. If you could become pregnant while taking this medicine, you should consider using a reliable means of contraception for approximately 1 week after the dose. If you become pregnant while taking this medicine, contact your doctor.

Driving and using machines: FLUCONAZOLE 150 can cause dizziness and seizures. Do not drive or operate machinery until you know how **FLUCONAZOLE 150** affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.
The following may interact with FLUCONAZOLE 150:

- Abrocitinib (used to treat atopic dermatitis (a type of eczema)).
- Antibiotics (rifabutin or rifampicin)
- Astemizole*or terfenadine* (used to treat allergies)
- Blood thinners (warfarin or similar drugs)
- Cimetidine or cisapride* (for control of heartburn)
- Cyclosporine or tacrolimus (used to prevent organ transplant rejection)
- Glyburide, glipizide or tolbutamide (medicines for diabetes)
- Ibrutinib (used to treat cancer)
- Ivacaftor (used to treat cystic fibrosis)
- Lemborexant (used to treat insomnia)

- Lurasidone (used to treat brain disorder)
- Midazolam or triazolam (used to help you sleep or for anxiety)
- Oral Contraceptives
- Phenytoin (used to control epilepsy)
- Prednisone (steroid used to treat skin, stomach, blood or breathing disorders)
- Statins (cholesterol lowering agents)
- Theophylline (used to control asthma)
- Tolvaptan (used to treat low blood sodium)
- Water pills (diuretics), such as hydrochlorothiazide
- Zidovudine (used to treat AIDS/HIV)

* not marketed in Canada

How to take FLUCONAZOLE 150:

Consult your doctor if this is your first yeast infection, or if you have a second yeast infection in less than 2 months after treating a prior infection.

Usual dose:

Adults (≥12 years old): Take **FLUCONAZOLE 150** by mouth as a one-time only dose, with or without food, or as directed by your doctor. DO NOT take more than one dose for this infection. If your symptoms have not improved within 3 days and disappeared in 7 days, contact your doctor.

Clearing a yeast infection does take time. Although **FLUCONAZOLE 150** is taken only once, **FLUCONAZOLE 150** therapy does not cure the infection in just one day, the medication remains active in your body for several days. Most patients can expect to see symptom relief begin within 24 hours after taking the capsule. As **FLUCONAZOLE 150** works to cure the infection, symptoms will lessen and eventually disappear.

Overdose:

If you think you, or a person you are caring for, have taken too much **FLUCONAZOLE 150**, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using FLUCONAZOLE 150?

These are not all the possible side effects you may have when taking **FLUCONAZOLE 150**. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, **FLUCONAZOLE 150** may cause some side effects.

The most common side effects are:

- Headache,
- Abdominal pain,
- Diarrhea,
- Nausea,
- Vomiting.

Most reported side effects were mild to moderate in nature.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Skin disorders: skin eruptions, new rash or irritations or allergy symptoms such as hives			✓
Liver problems: abdominal pain, dark urine, fever, light-colored stool, yellowing of the skin and eyes			✓
COMMON			
Heart problems: unstable or irregular heartbeat, chest pain, shortness of breath, dizziness, fainting			✓
RARE			
Severe allergic reactions (swelling of face, eyes, mouth, hands and feet)			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) 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.

Storage:

Store at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about FLUCONAZOLE 150:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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