PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-FLUCONAZOLE

Fluconazole Tablets

Tablets, 50 mg and 100 mg, Oral

House Standard

Antifungal Agent

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Date of Initial Authorization:
JUN 5, 2002

Date of Revision:
MAY 16, 2023

Submission Control Number: 273867

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	10/2022
9 DRUG INTERACTIONS	03/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Treatment

pms-FLUCONAZOLE (fluconazole) is indicated for the treatment of:

1. Oropharyngeal and esophageal candidiasis. pms-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

pms-FLUCONAZOLE is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.

1.1 Pediatrics (<18 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of pms-FLUCONAZOLE in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 7.1.3 Pediatrics.

1.2 Geriatrics

pms-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 pms-FLUCONAZOLE was administered prophylactically there was a greater incidence of drug discontinuation due to adverse reactions (4.3%) than in younger patients (1.7%).

2 CONTRAINDICATIONS

pms-FLUCONAZOLE (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole, to any of its excipients or to related azole compounds. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

pms-FLUCONAZOLE (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 2 hours of dosing. The terminal plasma elimination half-life is approximately 30 hours (range 20-50 hours).

The daily dose of pms-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.

4.2 Recommended Dose and Dosage Adjustment

RECOMMENDED DOSAGES IN ADULTS AND CHILDREN (also see 10 CLINICAL 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

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.

Recommended Treatment Guidelines		
Indication	**Adults**	**Children**
Oropharyngeal Candidiasis	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.
Esophageal Candidiasis	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.
Systemic Candidiasis (Candidemia and Disseminated Candidal Infections)	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.
Cryptococcal Meningitis	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.
Prevention of Recurrence of Cryptococcal Meningitis in Patients with AIDS	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 10 CLINICAL 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 2 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 pms-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/mm^3) should start pms-FLUCONAZOLE prophylaxis several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells/mm^3.

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 mg 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:

Daily Dose		
Creatinine Clearance (mL/min)	**Creatinine Clearance (mL/sec)**	**Recommended Dose (%)**
> 50	**> 0.83**	**100**
21-50 (no dialysis)	**0.35-0.83 (no dialysis)**	**50**
11-20 (no dialysis)	**0.18-0.34 (no dialysis)**	**25**
Hemodialysis	**Hemodialysis**	**100 after each hemodialysis**

Patients on hemodialysis should receive 100% of the recommended dose after each hemodialysis; 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.

Creatinine Clearance Calculations		
	mL/min	**mL/sec**
Males:	$\frac{\text{Weight (kg)} \times (140\text{-age})}{72 \times \text{serum creatinine (mg/100 mL)}}$	$\frac{\text{Weight (kg)} \times (140\text{-age})}{50 \times \text{serum creatinine (mcmol/L)}}$
Females:	0.85 × above value	0.85 × 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 0.45 for infants.)

4.5 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, the patient should skip the missed dose and go back to the regular dosing schedule. The patient should not double dose.

5 OVERDOSAGE

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

Symptoms: There have been reports of overdosage 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 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

Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
oral	Tablet / 50 mg and 100 mg	Croscarmellose Sodium, Dibasic Calcium Phosphate Anhydrous, FD&C Red no. 3 and no. 40 Lake Dye, Magnesium Stearate, Microcrystalline Cellulose and Povidone.

pms-FLUCONAZOLE 50 mg: Tablets are light pink, trapezoid, debossed "P" logo on one side and "50" on the other side. They are available in white HDPE bottles of 50 and 100 tablets.

pms-FLUCONAZOLE 100 mg: Tablets are light-pink, trapezoid, debossed "FCZ" on one side and "100" on the other. They are available in white HDPE bottles of 50 and 100 tablets.

7 WARNINGS AND PRECAUTIONS

Anaphylaxis

In rare cases, anaphylaxis has been reported.

Cardiovascular

QT Prolongation

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on an electrocardiogram (see 10.3 Pharmacokinetics - QT Prolongation and 9.4 Drug-Drug Interactions – Amiodarone and Drugs prolonging the QTc interval). During post-marketing surveillance, there have been very rare cases of QT prolongation and *torsades 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. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular arrhythmias and *torsades de pointes*. The potential for proarrhythmic events increases with co-administration of other drugs that prolong the QT interval such as some antiarrhythmics, antihistamines, psychotropic agents and antibacterials. Caution and careful monitoring should be used with concomitant administration of such drugs (see 9.4 Drug-Drug Interactions – Amiodarone and Drugs prolonging the QTc interval as well as 10.3

Pharmacokinetics - QT Prolongation).

Fluconazole should be administered with caution to patients with proarrhythmic conditions (see 9.4 Drug-Drug Interactions - Drugs prolonging the QTc interval and 8 ADVERSE REACTIONS).

Driving and Operating Machinery

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

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 while receiving fluconazole or when fluconazole was discontinued (see 9 DRUG INTERACTIONS).

CYP2C9, CYP2C19 and CYP3A4 metabolized drugs

Fluconazole is a moderate CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of the isoenzyme CYP2C19. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP 3A4 should be monitored (see 2 CONTRAINDICATIONS).

Hepatic/Biliary/Pancreatic

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 pms-FLUCONAZOLE therapy should be monitored for the development of more severe hepatic injury. pms-FLUCONAZOLE should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole.

Renal

Fluconazole should be administered with caution to patients with renal dysfunction (see 4.2 Recommended Dose and Dosage Adjustment).

Reproductive Health: Female and Male Potential

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

Sensitivity/Resistance

Superinfections

There have been reports of superinfection with *Candida* species other than *C. albicans*, which often have reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g., *C. krusei, C. auris*). Such infections may require alternative antifungal therapy.

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).

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

Skin

Dermatologic: Patients have rarely developed exfoliative skin disorders during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported.

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 pms-FLUCONAZOLE should be monitored closely and the drug discontinued if lesions progress.

7.1 Special Populations

7.1.1 Pregnant Women

pms-FLUCONAZOLE (fluconazole) should not be used in pregnant women except in patients with severe or potentially life-threatening fungal infections in whom pms-FLUCONAZOLE (fluconazole) 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 as well as observational studies that have suggested an increased risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with doses as low as 150 mg of fluconazole as a single or repeated dose during 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, arthrogryposis, and congenital heart disease.

These reported anomalies are similar to those seen in animal studies (see 16 NON-CLINICAL TOXICOLOGY).

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.

7.1.3 Pediatrics

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 10 CLINICAL PHARMACOLOGY) establishing dose proportionality between children and adults (see 4 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 8 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 7 WARNINGS AND PRECAUTIONS).

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.

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4,048 patients receiving fluconazole for 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, asparate aminotransferase increased, blood alkaline phosphatase increased.

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.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

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	Comparative Agent
	(N=577)	(N=451)
With any side effect	13.0	9.3
Vomiting	5.4	5.1

	Fluconazole	Comparative Agent
	(N=577)	(N=451)
Abdominal pain	2.8	1.6
Nausea	2.3	1.6
Diarrhea	2.1	2.2

8.3 Less Common Clinical Trial Adverse Reactions

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 7 WARNINGS AND PRECAUTIONS). 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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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 (>3xULN) 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 I).

TABLE I

LAB PARAMETER	#* OF PATIENTS	% ABNORMAL	# OF PATIENTS	% ABNORMAL
		BASELINE > 3xULN		BASELINE < 3xULN
AST	53	9.4	3007	4.2
ALT	65	3.1	2874	4.8
		HEPATITIS PATIENTS		NON-HEPATITIS
AST	160	10.6	2900	PATIENTS 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		NEVER RECEIVED IV
AST		IV FLUCONAZOLE		FLUCONAZOLE
ALT	144	5.6	2916	4.2
	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%).

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

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.

8.5 Post-Market Adverse Reactions

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, *torsades de pointes* (see 7 WARNINGS AND PRECAUTIONS - QT Prolongation).
Body As A Whole: asthenia, fatigue, fever, malaise and urticaria. Central Nervous System: seizures, dizziness.
Congenital and familial/genetic disorders: congenital abnormality (see 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women).
Dermatologic: alopecia, acute generalized exanthematous-pustulosis, face edema, exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necrolysis, dermatitis exfoliative (see 7 WARNINGS AND PRECAUTIONS), drug eruption including Fixed Drug Eruption, increased sweating, drug reaction with eosinophilia and systemic symptoms (DRESS) (see 7 WARNINGS AND PRECAUTIONS, Skin)
Endocrine disorders: adrenal insufficiency (see 7 WARNINGS AND PRECAUTIONS).
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: hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia. Musculoskeletal: myalgia.
Nervous System: tremor, insomnia, paresthesia, somnolence, vertigo. Other Senses: taste perversion.
Pregnancy, puerperium and perinatal conditions: abortion spontaneous (see 7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also a strong inhibitor of the isoenzyme CYP2C19. 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 coadministered 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.

9.4 Drug-Drug Interactions

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

Abrocitinib

In the presence of fluconazole (a strong inhibitor of CYP2C19, and moderate inhibitor of 2C9 and 3A4) exposure of abrocitinib active moiety was 2.5-fold higher (and abrocitinib 4.8-fold higher) compared to abrocitinib alone. Concomitant administration of pms-FLUCONAZOLE and abrocitinib is not recommended. If clinical judgment deems concomitant use of these necessary, reduce abrocitinib dose as instructed in abrocitinib prescribing information and exercise appropriate caution.

Alfentanil

A study observed a reduction in clearance and distribution volume as well as prolongation of T½ 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.

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).

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 1 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.

Antacid:
Administration of aluminum/magnesium/simethicone (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.

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.

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.

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, C_{max} by 20% to 32%, and increases $t_{½}$ 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 ± 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.

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Coumarin-Type or Indanedione Anticoagulants

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

and coumarin-type or indanedione anticoagulants is recommended.

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 pms-FLUCONAZOLE and cyclosporine. This combination may be used by reducing the dosage of cyclosporine depending on cyclosporine concentration.

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: –5 to 133%). The C_{min} increased 157% ± 96% (range: 33 to 360%). The apparent oral clearance decreased 45% ± 15% (range: –15 to –60%).

Cyclophosphamide

Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking into consideration the risk of increased serum bilirubin and serum creatinine. Caution should be exercised and patients should be monitored for increased toxicity of cyclophosphamide.

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 coadministering pms-FLUCONAZOLE and such agents (see 7 WARNINGS AND PRECAUTIONS - QT Prolongation). Patients should be carefully monitored.

Concomitant use of the following other medicinal products is contraindicated:

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsade de pointes.
Coadministration of fluconazole and pimozide is contraindicated (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 torsade 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 death. Coadministration of fluconazole and erythromycin is contraindicated (see 2 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 12 healthy volunteers, it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients 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 (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

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.

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 ± 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 the 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. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

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.

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.

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.

Methadone

Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

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.

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.

Olaparib

Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, the dose of Olaparib should be adjusted.

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.

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%).

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.

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 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.

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 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.

Phenytoin

Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving pms-FLUCONAZOLE and phenytoin is recommended.

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 ± SD increase in phenytoin AUC was 88% ± 68% (range: 16 to 247%). The absolute magnitude of this interaction is unknown because of the intrinsically nonlinear 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 up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and pms-FLUCONAZOLE concomitantly should be carefully monitored.

Rifampin

Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of pms-FLUCONAZOLE when it is administered with 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 ± 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.

Saquinavir

Fluconazole increases the AUC of saquinavir by approximately 50%, C_{max} by approximately 55% and decreases the 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 are 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 pms-FLUCONAZOLE concomitantly should be carefully monitored for tacrolimus associated adverse effects, especially nephrotoxicity.

Theophylline

Patients who are receiving high-dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving pms-FLUCONAZOLE, and therapy modified appropriately if signs of toxicity develop. Fluconazole increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving pms-FLUCONAZOLE and theophylline is recommended.

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.

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).

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.

Triazolam

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, C_{max} by 20-32% and increases t½ 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 pseudotumor cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole (CYP2C9, 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 8 healthy male subjects (CYP2C19 extensive metabolisers) resulted in an increase in C_{max}, and AUCτ, 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.

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.

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

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 ± 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.

Zidovudine

Fluconazole increases the C_{max} 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.

Plasma zidovudine concentrations were determined on two occasions (before and following fluconazole 200 mg daily for 15 days) in 13 volunteers with AIDS or AIDS-related complex (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.

9.5 Drug-Food Interactions

Interactions with food 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-α-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

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.

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.

<u>Pharmacokinetic/pharmacodynamic relationship</u>

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

10.2 Pharmacodynamics

The effects of fluconazole on the metabolism of carbohydrates, lipids, adrenal and gonadal hormones were assessed. Fluconazole appears to have no clinically significant effects on carbohydrate or lipid metabolism in man. In normal volunteers, fluconazole administration (doses ranging from 200 mg 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.

10.3 Pharmacokinetics

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 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 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.

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 20-50 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 50-400 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 5-10 days following oral doses of 50-400 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.

Distribution

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

Tissue or Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*
Cerebrospinal fluid+	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

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. The dose of pms-FLUCONAZOLE may need to be reduced in patients with impaired renal function (see 4 DOSAGE AND ADMINISTRATION). A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

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 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.

Special Populations and Conditions

- **Pediatrics**

In children, pharmacokinetic data {MEAN (% cv)} have been reported as follows:

Pharmacokinetic Data in Children					
Age Studied	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (Hours)	C_{max} (mcg/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) six 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 days later and 46.6 hours 12 days later.

The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients:

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.

- **Pregnancy and Breast-feeding**

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 that measured in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose, similar to that observed in maternal plasma (2.61 mg/L at 2.6 hours post-dose) and the elimination half-life from breast milk approximates the plasma elimination half-life of 30 hours.

QT Prolongation

Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4 (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS – QT Prolongation and 9 DRUG INTERACTIONS – Amiodarone and Drugs prolonging the QTc interval).

Animal

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

TABLE III

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[a] (% of dose)	79 (78)	--	72 (80)	91

Values in parentheses are from i.v. administration; all others are from oral administration.
[a:] 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).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

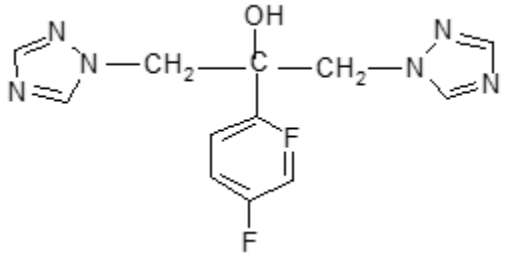
Proper name: fluconazole

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

Molecular formula: $C_{13}H_{12}F_2N_6O$

Molecular mass: 306.3 g / mol

Structural formula:



Physicochemical properties:

Description: Fluconazole is a white to off-white odourless crystalline powder, freely soluble in methanol, soluble in acetone, sparingly soluble in aqueous 0.1 M hydrochloric acid and ethanol, slightly soluble in water and saline, and very slightly soluble in hexane.

Solubility: Fluconazole is slightly soluble in water and freely soluble in methanol.

Melting Range: 136° to 140°C

pH Value: 3.11

pKa: 1.76

Octanol/Water Partition Coefficient: Log P = 0.5

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The data is not available.

14.2 Study Results

The data is not available.

14.3 Comparative Bioavailability Studies

Pivotal Comparative Bioavailability Studies

A two-way, crossover, blinded, single-dose, fasting, bioequivalence study of pms-FLUCONAZOLE 100 mg Tablets, was performed versus Pfizer Canada Inc.'s, DIFLUCAN® 100 mg Tablets, administered as 1 × 100 mg Tablet in 22 normal, healthy male subjects under a Fasting State. Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Fluconazole (1 × 100 mg) From measured data Geometric Mean (CV %) Arithmetic Mean (CV %)				
Parameter	**pms-FLUCONAZOLE**	**Diflucan®***	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	70,209 70,869.3 (14.1)	70,517 71,098.2 (13.1)	100	98 – 101
AUC_∞ (ng•h/mL)	93,748 95,270.9 (18.5)	93,513 95,100.8 (19.2)	101	98 – 103
C_{max} (ng/mL)	2,002.3 2,018.3 (13.3)	1,979.5 1,996.6 (13.6)	101	98 –105
T_{max} § (h)	1.01 (0.67-4.00)	1.51 (0.67-6.00)		
$T_{½\ el}$ € (h)	36.27 (15.49)	35.94 (20.07)		

* Diflucan® was manufactured by Pfizer (Canada) and was purchased in Canada.

§ Expressed as median (range) only.

€ Expressed as arithmetic mean only.

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* 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**

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 IV).

TABLE IV **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**

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 ED50 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 ED50 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 ED50 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 ED50 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 ED50 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 meclorethamine (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 x 105 yeast cells, fluconazole (10 to 50 mg/kg p.o.) produced a dose-dependent reduction of between approximately 102 and 104 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 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 mechlorethamine and systemically infected with *Aspergillus fumigatus* die 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.

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

General Toxicology:

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).

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.

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.

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

Genotoxicity: 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.

Reproductive and Developmental Toxicology:

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), 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.

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 labor, and did not impair the development, behavior or fertility of the offspring. The fetuses from the dams sacrificed on day 20 post-insemination (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, behavior 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 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 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 postpartum 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.

Juvenile Toxicity:

Acute Toxicity

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 behavior. 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.

Subacute/Chronic Toxicity

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.

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 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 IC50 for inhibition was 0.55 mcM for ketoconazole and 8-10 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 [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 mcg/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 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-ß-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 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 (IC50 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

DIFLUCAN®, Tablets 50 mg and 100 mg, submission control 268015, Product Monograph, Pfizer Canada ULC. (FEB 7 2023)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-FLUCONAZOLE

fluconazole tablets

Read this carefully before you start taking pms-FLUCONAZOLE 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 pms-FLUCONAZOLE.

What is pms-FLUCONAZOLE used for?
pms-FLUCONAZOLE is used to treat fungal infections. These are infections caused by fungi, including yeasts. pms-FLUCONAZOLE can also be used to stop you from getting a fungal infection.

How does pms-FLUCONAZOLE work?
pms-FLUCONAZOLE belongs to a group of medicines called antifungals. It helps to stop fungal growth.

What are the ingredients in pms-FLUCONAZOLE?
Medicinal ingredients: Fluconazole
Non-medicinal ingredients: Croscarmellose Sodium, Dibasic Calcium Phosphate Anhydrous, FD&C Red No. 3 and No. 40 Lake Dye, Magnesium Stearate, Microcrystalline Cellulose and Povidone.

pms-FLUCONAZOLE comes in the following dosage forms:
tablets: 50 mg and 100 mg

Do not use pms-FLUCONAZOLE if:
- you have ever had an allergic reaction to fluconazole or any of the other ingredients of pms-FLUCONAZOLE (see What are the ingredients in pms-FLUCONAZOLE?)
- you have ever had an allergic reaction to other medicines you have taken to treat a fungal infection.
- you are taking any of the following:
  - Erythromycin (an antibiotic for treating infections)
  - Pimozide (for treating schizophrenia)
  - Quinidine (used for irregular heartbeats)

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

- have liver or kidney problems
- have abnormal levels of potassium, calcium or magnesium in your blood
- have heart problems including problems with your heart rhythm such as QT prolongation

Other warnings you should know about:

Pregnancy and Breastfeeding:

- Do not get pregnant while you are taking pms-FLUCONAZOLE. If you are pregnant, think you might be pregnant or are thinking of becoming pregnant talk to your healthcare professional.
- pms-FLUCONAZOLE can harm your unborn baby. It can also cause you to have a miscarriage.
- pms-FLUCONAZOLE must only be used in pregnancy to treat life-threatening fungal infections.
- If you are able to get pregnant you must use effective birth control while you are taking pms-FLUCONAZOLE and for 1 week after you stop taking pms-FLUCONAZOLE. Talk to your healthcare professional about the birth control options that are right for you.
- You should not breastfeed while you are taking pms-FLUCONAZOLE. Fluconazole passes into breastmilk. Talk to your healthcare professional if you are breastfeeding or planning to breastfeed.

Serious skin problems: Serious skin problems, including **Stevens-Johnson syndrome**, and **Drug reaction with eosinophilia and systemic symptoms (DRESS)** have occurred in people taking pms-FLUCONAZOLE. These skin conditions are more likely to happen if you have AIDS or cancer. In rare cases they have been fatal. If you get a rash while taking pms-FLUCONAZOLE, tell your healthcare professional immediately. See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

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

- Abrocitinib (used to treat a skin condition called “atopic dermatitis.” This is a type of eczema).
- Alfentanil, fentanyl or methadone (used to treat pain)
- Amiodarone (used for irregular heartbeats)

- 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 or Indanedione 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)
- Ibrutinib (for treating some forms of cancer)
- Ivacaftor (for treating cystic fibrosis)
- Lemborexant (for treating insomnia)
- Lurasidone (for treating brain disorders)
- 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
- Olaparib (for treating some forms of cancer)
- 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)
- Tolvaptan (used to treat some type of kidney disease)
- 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)

How to take pms-FLUCONAZOLE:
Take pms-FLUCONAZOLE as directed by your healthcare professional.

Usual dose:

Adults: 100 to 200 mg daily.

Your healthcare professional will decide on your dose and how long you should take pms-FLUCONAZOLE based on the type of infection being treated.

Children: Your healthcare professional will decide on the dose and how long your child should take pms-FLUCONAZOLE based on your child's weight and the type of infection being treated.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-FLUCONAZOLE, contact a 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.

What are possible side effects from using pms-FLUCONAZOLE?
These are not all the possible side effects you may have when taking pms-FLUCONAZOLE. If you experience any side effects not listed here, tell your healthcare professional.
Side effects may include:

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

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 problems (Stevens-Johnson syndrome): rash, blisters, itching all over the body, reddening of the skin or itchy red spots, swelling of eyelids, face or lips, peeling or lost skin			✓
- Drug reaction with eosinophilia and systemic symptoms (DRESS): severe rash, fever, swollen lymph glands		✓	

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	
Liver problems: abdominal pain, dark urine, fever, light-colored stool, yellowing of the skin and eyes			✓
COMMON			
Heart problems (QT prolongation, torsade de pointes): unstable or irregular heartbeat, chest pain, shortness of breath, dizziness, fainting			✓
Allergic reaction: swelling of the face, throat, mouth, extremities, difficulty in breathing, rash or itching			✓

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/adverse-reaction-reporting.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 between 15°C and 30°C.

Keep out of reach and sight of children.

If you want more information about pms-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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by contacting the sponsor, Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

Last Revised: May 16, 2023