PRODUCT MONOGRAPH

NOVO-FLUCONAZOLE TABLETS
(fluconazole)

50, 100 and 150 mg Tablets

FLUCONAZOLE INJECTION
(fluconazole)

Injection 100 mL vial (2 mg/mL intravenous infusion)
Injection 100 mL and 200 mL Cryovac bags (2 mg/mL intravenous infusion)

Antifungal Agent

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THERAPEUTIC CLASSIFICATION

Antifungal

ACTION AND CLINICAL PHARMACOLOGY

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14-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.

A two-way, single-dose, fasting comparative bioavailability study was performed on two 100 mg fluconazole products, NOVO-FLUCONAZOLE 100 mg tablets and DIFLUCAN® 100 mg tablets. The Pharmacokinetic data calculated for fluconazole in the NOVO-FLUCONAZOLE and DIFLUCAN® tablet formulations is tabulated in Table 1.

Table 1

	Geometric Mean Arithmetic Mean (C.V.)		
	Novo-Fluconazole (2 x 100 mg)	Diflucan®** (2 x 100 mg)	% Ratio of Geometric Means
AUC_T (μg·hr/mL)	192.48 193.84 (11.25)	186.79 186.59 (8.7)	103
AUC_{0-72} (μg·hr/mL)	151.41 151.85 (10.08)	145.47 145.83 (7.44)	104
AUC_I (μg·hr/mL)	202.35 203.5 (11.61)	196.37 196.37 (8.35)	103
C_{max} (μg/mL)	4.35 4.38 (12.47)	4.3 4.39 (17.65)	101
T_{max}* (hr)	1.31 (0.94)	1.86 (1.48)	---
$T_{1/2}$* (hr)	36.37 (4.85)	36.78 (4.12)	------

* For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).
** Diflucan® 100 mg Tablets, Pfizer Canada Inc., Canada and purchased in Canada.

INDICATIONS AND CLINICAL USES

Treatment

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

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

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Prophylaxis:

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

CONTRAINDICATIONS

NOVO-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) are contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing NOVO-FLUCONAZOLE and FLUCONAZOLE INJECTION to patients with hypersensitivity to other azoles.

Co-administration of terfenadine is contraindicated in patients receiving NOVO-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study (see PRECAUTIONS).

Co-administration of cisapride is contraindicated in patients receiving NOVO-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) (see PRECAUTIONS).

WARNINGS

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

Anaphylaxis: In rare cases, anaphylaxis has been reported.
Dermatologic: Patients have rarely developed exfoliative skin disorders during treatment with fluconazole. In patients with serious underlying diseases (predominantly AIDS and malignancy) those have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with fluconazole should be monitored closely and the drug discontinued if lesions progress.

PRECAUTIONS

QT Prolongation

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions. (see **PRECAUTIONS - Drug Interactions – Drugs prolonging the QTc interval** and **ADVERSE REACTIONS**).

Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high dose (400-800 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. NOVO-FLUCONAZOLE and FLUCONAZOLE INJECTION (fluconazole) are not recommended in pregnant women unless the potential benefit outweighs the potential risk to mother and fetus.

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

organogenesis and parturition.

Use in Women of Child-bearing Potential
Since the teratologic effects of fluconazole in humans are unknown, women taking NOVO-FLUCONAZOLE and FLUCONAZOLE INJECTION should consider using adequate contraception (see USE IN PREGNANCY).

There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high dose (400 - 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. Since there are no adequate studies in pregnant women to assess the potential for fetal risk, fluconazole should not be used in pregnant women unless the potential benefit outweighs the potential risk to the fetus.

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

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

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

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

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

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

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

Use in Elderly

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

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

Superinfections

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

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

Drug Interactions

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

Benzodiazepines (Short Acting)

Following oral or intravenous administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psycomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy, such as midazolam or triazolam, is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patient should be appropriately monitored.

Cimetidine

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

Coumarin-Type Anticoagulants

In a clinical trial, there was a significant increase in prothrombin time response (area under the prothrombin time-time curve) following a single dose of warfarin (15mg) administered to 13 normal male volunteers following oral fluconazole 200mg administered daily for 14 days as compared to the administration of warfarin alone. There

was a mean ± SD increase in the prothrombin time response (area under the prothrombin time-time curve) of 7% ± 4% (range: -2 to 13%). Mean is based on data from 12 subjects as one of 13 subjects experienced a 2-fold increase in his prothrombin time response.

During the post-marketing experience, as with some azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin.

Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended.

Cyclosporine

Cyclosporine AUC and C_{max} were determined before and after the administration of fluconazole 200 mg daily for 14 days in eight renal transplant patients who had been on cyclosporine therapy for at least 6 months and on a stable cyclosporine dose for at least 6 weeks. There was a significant increase in cyclosporine AUC, C_{max}, C_{min} (24-hour concentration), and a significant reduction in apparent oral clearance following the administration of fluconazole. The mean ± SD increase in AUC was 92 % ± 43 % (range: 18 to 147 %). The C_{max} increased 60 % ± 48 % range (range: -5 to 133 %). The C_{min} increased 157 % ± 96 % (range: 33 to 360 %). The apparent oral clearance decreased 45 % ± 15 % (range: -15 to -60 %). Fluconazole administered at 100 mg daily dose does not affect cyclosporine pharmacokinetic levels in patients with bone marrow transplants. Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving fluconazole and cyclosporine.

Drugs prolonging the QTc interval:

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

Astemizole: Definitive interaction studies with fluconazole have not been conducted. The use of fluconazole may be associated with elevations in serum levels of astemizole. Caution should be used when co-administering fluconazole with astemizole. Patients should be carefully monitored.

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

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to

prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. In one study, 6 healthy volunteers received terfenadine 60mg BID for 15 days. Fluconazole 200mg was administered daily from days 9 through 15. Fluconazole did not affect terfenadine plasma concentrations. Terfenadine acid metabolite AUC increased 36% ± 36% (range: 7 to 102%) from day 8 to day 15 with the concomitant administration of fluconazole. There was no change in cardiac repolarization as measured by Holter QTc intervals. However, another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. Therefore the combined use of fluconazole at doses of 400mg or higher with terfenadine is contraindicated (see CONTRAINDICATIONS). Patients should be carefully monitored if they are being concurrently prescribed fluconazole at multiple doses lower than 400mg/day with terfenadine.

Hydrochlorothiazide

Concomitant oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and C_{max} compared to fluconazole given alone. There was a mean ± 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%).

Oral Contraceptives

In pharmacodynamic studies, single and multiple 50 mg oral doses of fluconazole produced an overall mean increase in ethinyl estradiol or levonorgestrel pharmacokinetics in healthy women taking oral contraceptives. At 200 mg of fluconazole daily, the AUCs of ethinyl estradiol and levonorgestrel were increased, 40% and 24%, respectively.

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.

Oral Hypoglycemics

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

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

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

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

Clinically significant hypoglycemia may be precipated 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.

Phenytoin

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

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

Rifabutin

There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

Rifampin

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

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

Tacrolimus

There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were co-administered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

Theophylline

The pharmacokinetics of theophylline were determined from a single intravenous dose of aminophylline (6 mg/kg) before and after the oral administration of fluconazole 200 mg daily for 14 days in 16 normal male volunteers. There were significant increases in theophylline AUC, C_{max}, and half-life with a corresponding decrease in clearance. The mean ± SD theophylline AUC increased 21% ± 16% (range: -5 to 48%). The C_{max} increased 13% ± 17% (range: -13 to 40%). Theophylline clearance decreased 16% ± 11% (range: -32 to 5%). The half-life of theophylline increased from 6.6 ± 1.7 hours to 7.9 ± 1.5 hours. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and therapy modified appropriately if signs of toxicity develop.

Zidovudine

Plasma zidovudine concentrations were determined on two occasions (before and following fluconazole 200 mg daily for 15 days) in 13 volunteers with AIDS or ARC who were on a stable zidovudine dose for at least two weeks. There was a significant increase in zidovudine AUC following the administration of fluconazole. The mean ± SD increase in AUC was 20% ± 32% (range: -27 to 104%). The metabolite, GZDV, to parent drug ratio significantly decreased after the administration of fluconazole, from 7.6 ± 3.6 to 5.7 ± 2.2. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

Drugs exhibiting no significant pharmacokinetic interactions with fluconazole:

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

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

Drug/Laboratory Test Interactions

None known.

ADVERSE REACTIONS

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

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

Adverse clinical events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The two most serious adverse clinical events noted during clinical trials with fluconazole were:
1. Exfoliative skin disorders
2. Hepatic necrosis.

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

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4,048 patients receiving fluconazole for seven 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%).

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

Skin and Appendages: pruritus.
Musculoskeletal: myalgia.
Central and Peripheral Nervous System: convulsions, dizziness, paresthesia, tremor, vertigo.
Autonomic Nervous System: dry mouth, increased sweating.
Psychiatric: insomnia, somnolence.
Gastrointestinal: anorexia, constipation, dyspepsia, flatulence.
Liver and Biliary System: cholestasis, hepatocellular damage, jaundice.
Special Senses: taste perversion.
Hematopoietic: anemia.
General: fatigue, malaise, asthenia, fever.
Immunologic: In rare cases, anaphylaxis has been reported.
In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post- marketing experience):
Cardiovascular: QT prolongation, torsade de pointes (see **PRECAUTIONS – QT Prolongation**).
Central and Peripheral Nervous System: seizures.

Dermatologic: alopecia, exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necrolysis (see WARNINGS).
Hematopoietic and Lymphatic: leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.
Body As A Whole: anaphylaxis including angioedema, face edema, pruritus and urticaria.
Liver/Biliary: hepatic failure, hepatitis.
Metabolic: hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Laboratory Test Abnormalities

Liver Function

Clinically significant increases were observed in the following proportions of patients: AST 1%, ALT 1.2%, alkaline phosphatase 1.2%, total bilirubin 0.3%. The incidence of elevated serum aminotransferases was independent of age or route (p.o. or i.v.) of administration but was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid or oral hypoglycemic agents. Clinically significant increases also were more frequent in patients who: 1) had AST or ALT elevations greater than three times the upper limit of normal (>3 X ULN) at the time of entering the study (baseline), 2) had a diagnosis of hepatitis at any time during the study and, 3) were identified as alcohol abusers. The overall rate of serum aminotransferase elevations of more than 8 times the upper limit of normal was approximately 1% in patients treated with fluconazole during clinical trials. (See Table 2).

Table 2

Lab Parameter	*Number of Patients	% Abnormal	% Drug-Related	*Number of Patients	% Abnormal	% Drug-Related
		Baseline >3 X ULN			Baseline < 3 X ULN	
AST	53	9.4	3.8	3007	4.2	0.8
ALT	65	3.1	0.0	2874	4.8	1.0
		Hepatitis Patients			Non-Hepatitis Patients	
AST	160	10.6	1.9	2900	3.9	0.8
ALT	140	11.4	2.1	2799	4.4	1.0
		Alcohol Abuse			Non-Alcohol Abuse	
AST	42	9.5	2.4	3018	4.2	0.9
ALT	40	10.0	2.5	2899	4.7	1.0
		Received I.V. Fluconazole			Never Received I.V.Fluconazole	
AST	144	5.6	1.4	2916	4.2	0.9
ALT	139	5.0	0.7	2800	4.7	1.0
		≥ 65 Years Old			< 65 Years Old	
AST	277	4.3	1.1	2783	4.3	0.9
ALT	258	3.9	1.2	2681	4.8	1.0

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

Renal Function

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

Hematological Function

Clinically meaningful deviations from baseline in hematologic values which were possibly related to fluconazole were observed in the following proportions of patients: hemoglobin (0.5%), white

blood cell count (0.5%) and total platelet count (0.6%).

CHILDREN:
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% of patients due to laboratory test abnormalities.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

Oral (tablets) and Intravenous Administration
Fluconazole is well absorbed and excreted predominantly unchanged in urine following oral administration in man. The oral bioavailability is essentially complete (greater than 90%) and is independent of dose. Peak plasma concentrations after oral administration are attained rapidly, usually within two (2) hours of dosing. **Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral tablets and intravenous administration.** The terminal plasma elimination half-life is approximately 30 hours (range 20-50 hours).

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

Recommended Dosages in Adults and Children (see pharmacology):
Treatment

Loading Dose

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

Dosage Equivalency Scheme (see Table 3)

Table 3

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.

Table 4

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

Neonates

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

Prophylaxis in Adult Patients

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

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

Dosage in Patients with Impaired Renal Function

Adults:

Fluconazole is cleared primarily by renal excretion as unchanged drug. In patients with impaired renal function, an initial loading dose of 50 to 400 mg should be given (for children, see below). After the loading dose, the daily dose (according to indication) should be based on the following table (see Table 5):

Table 5

CREATININE CLEARANCE (mL/min)	CREATININE CLEARANCE (mL/sec)	PERCENT 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%
Regular hemodialysis	Regular hemodialysis	100% after each dialysis

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

Table 6

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

Children:

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

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

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

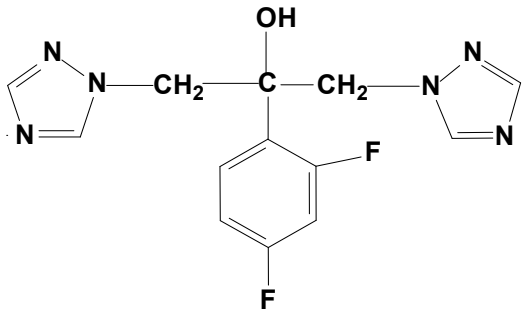
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Fluconazole

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

Structural Formula:



Molecular Formula: $C_{13}H_{12}N_6OF_2$ Molecular Weight: 306.27

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

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

COMPOSITION

NOVO-FLUCONAZOLE TABLETS: Active ingredient: Each tablet contains 50 mg or 100 mg or 150 mg of fluconazole. Non-medicinal ingredients: dibasic calcium phosphate anhydrous, croscarmellose sodium, microcrystalline cellulose, FD & C Red #40 Aluminum Lakes (alumina hydrate base), povidone, colloidal silicon dioxide, magnesium stearate.

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

STABILITY AND STORAGE RECOMMENDATION

NOVO-FLUCONAZOLE TABLETS: Store bottles between 15°- 30°C. Store unit dose packages between 15°- 25°C and protect from high humidity.

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

DIRECTIONS FOR USE

FLUCONAZOLE INJECTION

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

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

Connect an intravenous giving set to the vial of FLUCONAZOLE INJECTION solution and also insert a venting set through the stopper. Infuse FLUCONAZOLE INJECTION for intravenous solution at a maximum rate of 200 mg/hour. Flush FLUCONAZOLE INJECTION intravenous solution remaining in the giving set with sterile normal saline. Because FLUCONAZOLE INJECTION is available as a dilute saline solution, consideration should be given to the rate of fluid administration in patients requiring sodium or fluid restriction.
Fluconazole Injection in cryovac flexible infusion bag with spike port is intended only for intravenous infusion using sterile equipment. The intravenous infusion of fluconazole should be administered at a maximum rate of approximately 200 mg/hour given as a continuous infusion.

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

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

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

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

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

Incompatibility

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

Compatibility

Administration sets ("giving" sets).

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

AVAILABILITY OF DOSAGE FORMS

NOVO-FLUCONAZOLE is available as a four-sided, pink 50 mg compressed tablet, containing 50 mg of fluconazole, engraved with '**N**' on one side and '**50**' on the other. Supplied in bottles of 50, 100, 500 and 1000 and unit dose boxes of 100.

NOVO-FLUCONAZOLE is available as a four-sided, pink 100 mg compressed tablet, containing 100 mg of fluconazole, engraved with '**N**' on one side and '**100**' on the other. Supplied in bottles of 50, 100, 500 and 1000 and unit dose boxes of 100.

NOVO-FLUCONAZOLE is available as a round pink, bevelled edge, 150 mg compressed tablet, containing 150 mg of fluconazole, engraved with 'novo' on one side and '150' on the other. Supplied in bottles of 50, 100, 500 and 1000 and unit dose boxes of 100.

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

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 immuosuppressed animals.

In Vitro Studies

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

Table 7
The mean MIC* (μg/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 ED_{50} at 2 days was 0.08 mg/kg in mice and 0.22 mg/kg in rats. Fluconazole was 20 to 100-fold more potent than ketoconazole in these acute infections. The intravenous ED_{50} of fluconazole in mice was 0.06 mg/kg at 2 days, which was comparable to that (0.07 mg/kg) for amphotericin B. However, fluconazole was less active than amphotericin B after 5 days.

In a less acute model, untreated mice die within 7-25 days. After oral therapy once daily for 10 days, the ED_{50} 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 at 1, 4, and 24 hours post-infection, the ED_{50} values for fluconazole in such animals 2 and 5 days post-infection were 0.39 mg/kg and 0.88 mg/kg, respectively. Corresponding values for ketoconazole were 41.0 mg/kg and >50 mg/kg respectively.

Mice receiving daily dexamethasone are twice as sensitive to a less acute infection than normal animals and untreated controls die within 10 days. Oral therapy for 10 days gave ED_{50} 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 10^5 yeast cells, fluconazole (10 to 50 mg/kg p.o.) produced a dose-dependent reduction of between approximately 10^2 and 10^4 in the number of cryptococcal cells per g of lung tissue compared with the lung burden in control animals. In this respect, fluconazole at 50 mg/kg p.o. was considerably more active than 50 mg/kg p.o. of ketoconazole and as effective as 1 mg/kg i.p. amphotericin B.

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

Systemic Aspergillosis in Normal Mice

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

Systemic Aspergillosis in Immunosuppressed Mice

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

Development of Resistance and Cross-Resistance to Fluconazole

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

Significant fungistatic activity of fluconazole was observed against ketoconazole-resistant *Candida albicans* in a neutropenic rabbit model although doses of the order of 80 mg/kg were required. In another study, however, a strain of *Candida albicans* isolated from a patient with chronic mucocutaneous candidosis who had relapsed during treatment with ketoconazole was not

only cross-resistant to all azole antifungals *in vitro* but also in animal models *in vivo*.

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

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

PHARMACOLOGY

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

HUMAN Adults

Absorption

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

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

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

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

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

Pharmacokinetics in children

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

Table 8

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

Clearance corrected for body weight was not affected by age in these studies. Mean body clearance in adults is reported to be 0.23 mL/min/kg (17%).

In premature newborns (gestation age 26 to 29 weeks), the mean (% cv) clearance within 36 hours of birth was 0.18 mL/min/kg (35%, n=7), which increased with time to a mean of 0.218 mL/min/kg (31%, n=9) 6 days later and 0.333 mL/min/kg (56%, n=4) 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours 6 days later and 46.6 hours 12 days later.

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

Table 9

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

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

Distribution

The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11 to 12%) and is constant over the concentration range tested (0.1mg/L to 10 mg/L). This degree of protein binding is not clinically meaningful. Following either single- or multiple-oral doses for up to 14 days, fluconazole penetrates into all body tissues and fluids studied (see Table 10). In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations regardless of dose, route, or duration of dosing. In patients with bronchiectasis, sputum concentrations of fluconazole following a single 150 mg oral dose were equal to plasma concentrations at both 4 and 24 hours post dose. In patients with fungal

meningitis, fluconazole concentrations in the CSF (cerebrospinal fluid) are approximately 80% of the corresponding plasma concentrations. Whole blood concentrations of fluconazole indicated that the drug freely enters erythrocytes and maintains a concentration equivalent to that of plasma.

Table 10

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 and Excretion

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

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

Pharmacodynamics

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

Animal

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

Table 11

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

Values in parentheses are from intravenous 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).

General

The general pharmacological properties of fluconazole were investigated in a variety of *in vitro* and *in vivo* test. 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 μM, fluconazole did not stimulate intestinal muscle directly or show antimuscarinic or antihistaminic activity on the isolated guinea pig ileum.

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

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

TOXICOLOGY

a) **Acute Toxicity**

Adult animals

Fluconazole had extremely low toxicity when administered orally in single doses to male and female mice and rats, no deaths occurred at doses below 1000 mg/kg in either species. The first clinical signs noted were incoordination and decreased activity and respiration at doses greater than 500 mg/kg in mice, while only decreased activity was seen in rats at the 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 and female mice at 200 mg/kg, in rats at 165 mg/kg or in dogs at 100 mg/kg. Clinical signs lasting up to 5 to 7 hours included ataxia, exophthalmia, decreased activity and decreased respiration. Dogs which received single intravenous doses of 100 mg/kg showed only transient clinical signs (ataxia, decreased spontaneous movement and decreased respiration).

Neonatal animals

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

At necropsy the liver and/or lungs of these animals were congested.

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

b) **Subacute/Chronic Toxicity**

Adult animals

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

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

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

Neonatal animals

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

Fluconazole was given wither 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 100mg/kg/day.

Microscopically, hepatocellular hypertrophy was found in some of the rats given 50mg/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 100mg/kg/day. There were no findings in any of the animals given 10 or 30 mg/kg/day intraperitoneally.

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

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

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

c) **Cardiotoxicity**

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

d) **Carcinogenicity**

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

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

e) **Mutagenicity**

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

f) **Reproduction and Teratology**

General Fertility (Segment I and III) in rats:

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

Teratology studies (Segment II) in rats:

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

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

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

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

In another study, fluconazole was given orally on days 5-15 of gestation at dose levels of 80, 160 and 320 mg/kg. The vehicle used (Polyethylene Glycol, PEG-400) differed from the vehicle used in earlier studies with fluconazole. It caused maternal effects (an impairment of body weight and food consumption) in all dose groups, with a further drug-related effect being superimposed at the high dose level. Fluconazole, at all dose levels, resulted in an increased number of dead fetuses and resorption sites, and a decreased birth weight of pups. At 320 mg/kg, maternal toxicity was evidenced by decreased food consumption and a reduced increase in body weight. At all dose

levels, teratogenicity was evidenced by the presence of multiple visceral and skeletal malformations. Macroglossia, brachygnathia and cleft palate were the main major malformations which showed an increased incidence following dosing with fluconazole. Brachygnathia and cleft palate were increased at doses of 160 and 320 mg/kg while the increase in macroglossia was apparent from 80 mg/kg onwards. Other less commonly observed malformations at 320 mg/kg were those of the eyelids (ablepharia) and ears (bifid ear). A very high incidence of rudimentary 14th ribs, indicating an interference with fetal growth, was observed at all dose levels of fluconazole.

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

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

Peri and post-natal study (Segment III) in rats:
Dams were treated intravenously from day 17 of gestation to day 21 post-partum with 5, 20 or 40 mg/kg. This parenteral study confirmed the trend noted in the Segment I study of a delay in the onset of parturition. These disturbances of parturition were reflected in an increase in the number of litters with still-born pups and a slight decrease in pup survival at day 4 in the middle and high dose groups.

f) **Special Toxicity Studies**

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

g) **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 ß-estradiol and progesterone. The results show that both fluconazole and ketoconazole affected steroid metabolism. Fluconazole produced a lower estradiol level at both doses at 3 hours but only at the higher dose at 24 hours. Ketoconazole lowered estradiol levels at both doses at 3 hours only. Fluconazole, on the other hand, lowered progesterone levels only at the higher dose at 24 hours, while ketoconazole lowered it at both time points at both doses.

In vitro inhibition of estradiol synthesis was also measured in a broken cell preparation of pregnant rat ovary. The IC_50 for inhibition was 0.55 μM for ketoconazole and 8-10 μM for fluconazole. Thus, fluconazole is a much weaker inhibitor of estradiol synthesis.

Effects on Host Defense Mechanisms *In Vitro*

Fluconazole at concentrations of 5, 10 and 20 μg/mL, had little effect (3.4, 5.6 and 1.9% inhibition, respectively) on the destruction of [3H]-uridine-labeled *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 μg/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 μg/mL, fluconazole had little effect on the proliferation of concanavalin A and lipopolysaccharide-stimulated mouse spleen lymphocytes as measured by the uptake of [3H]-thymidine. In contrast, ketoconazole at concentrations up to and including 8 μg/mL, significantly reduced the uptake of [3H]-thymidine in the presence of both mitogens.

Effects on Key Endocrine Organs

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

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

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

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

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