PRODUCT MONOGRAPH

NU-FLUCONAZOLE-150
(Fluconazole)
Capsules, 150 mg

ANTIFUNGAL AGENT

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Control#: 133358

PRODUCT MONOGRAPH

NAME OF DRUG

NU-FLUCONAZOLE-150
(Fluconazole)
Capsules, 150 mg

THERAPEUTIC CLASSIFICATION

Antifungal Agent

ACTIONS AND CLINICAL PHARMACOLOGY

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

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

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

Summary Table of the Comparative Bioavailability Data **Fluconazole (Dose: 150 mg) From Measured Data**			
	Geometric Mean **Arithmetic Mean (CV%)**		**Ratio of Geometric**
Parameter	**NU-FLUCONAZOLE-150**	**Diflucan 150®†**	**Means**
$AUC_{0\text{-}72h}$ (μg·hr/mL)	87.2 89.9 (20.4)	89.6 92.3 (20.8)	97.3
AUC_I (μg·hr/mL)	141.9 147.3 (21.5)	140.8 144.8 (21.8)	100.8
C_{max} (μg/mL)	2.26 2.29 (19.1)	2.76 2.76 (15.4)	81.8
T_{max} (h)*	5.33 (60.4)	1.67 (45.1)	--
$t_{½}$ (h)*	44.6 (27.4)	42.1 (21.8)	--

*Arithmetic means only (CV%).

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

INDICATIONS AND CLINICAL USE

Fluconazole capsules are indicated for the oral treatment of:

- Vaginal candidiasis (yeast infections due to *Candida*).

The diagnosis of vaginal candidiasis should be confirmed by KOH smears and/or cultures before initiating therapy with fluconazole capsules.

CONTRAINDICATIONS

Fluconazole capsules 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 fluconazole to patients with hypersensitivity to other azoles. Coadministration of terfenadine is

contraindicated in patients receiving fluconazole at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study (see PRECAUTIONS).

WARNINGS

Anaphylaxis

In rare cases, anaphylaxis has been reported.

Hepatic Injury

In the treatment of systemic infections multiple doses of fluconazole have been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury.

Dermatologic

In rare cases, during the treatment of systemic infections, patients have developed exfoliative skin disorders during treatment with fluconazole.

Cisapride

There have been reports of cardiac events including torsades de pointes in patients receiving concomitant administration of fluconazole with cisapride. Patients should be carefully monitored if fluconazole is to be coadministered with cisapride (see PRECAUTIONS).

PRECAUTIONS

General

The convenience of the single oral dose fluconazole regimen for the treatment of vaginal yeast infections **should be weighed against the acceptability of a higher incidence of drug-related adverse events** with fluconazole (26%) versus intravaginal agents (16%) in

comparative clinical studies where no difference in efficacy was demonstrated (see ADVERSE REACTIONS).

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

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 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 3 months or longer. Fluconazole should not be used in pregnant women unless the potential benefit outweighs the potential risk to the 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 25 mg/kg. 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 to 320 mg/kg (approximately 10 to 40x the maximum recommended human dose) embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal 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 fluconazole for vaginal candidiasis 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 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 3 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 and Adolescents

The safety and effectiveness of fluconazole 150 mg capsules in the treatment of vaginal candidiasis in patients under 18 years of age have not been established.

Drug Interactions

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

Oral Contraceptives: Oral contraceptives were administered as a single dose both before and after the oral administration of fluconazole 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of fluconazole. The mean increase in ethinyl estradiol AUC was 6% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

Twenty-five normal females received daily doses of both 200 mg fluconazole or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving fluconazole during one cycle and placebo during the other. The order of study treatment was random. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (day 10) of both cycles. Following

administration of 200 mg of fluconazole, the mean percentage increase of AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyl estradiol compared to placebo was 38% (range: -11 to 101%). Both of these increases were statistically significantly different from placebo.

Drugs Prolonging the QTc Interval: The use of fluconazole in patients concurrently taking drugs metabolized by the cytochrome P450 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. Patients should be carefully monitored.

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

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 coadministering fluconazole with astemizole. Patients should be carefully monitored.

Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were coadministered. Therefore, caution should be used when co-administering fluconazole with cisapride. Patients should be carefully monitored (see WARNINGS).

Theophylline: The pharmacokinetics of theophylline were determined from a single i.v. 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.

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 2 hours after a single dose of cimetidine 400 mg to 6 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 to 900 mg i.v. 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.

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.

Cyclosporine: Cyclosporine AUC and C_{max} were determined before and after the administration of fluconazole 200 mg daily for 14 days in 8 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%). Fluconazole administered at 100 mg daily dose does not affect cyclosporine pharmacokinetic levels in patients with bone marrow transplants. Flucona-zole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful

monitoring of cyclosporine concentrations and serum creatinine is recom-mended in patients receiving fluconazole and cyclosporine.

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

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.

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.

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 Hypoglycemics: The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycemic agents tolbutamide, glipizide, and glyburide were evaluated in 3 placebo-controlled studies in normal volunteers. All subjects received the sulfonylurea alone as a single dose and again as a single dose following the administration of fluconazole 100 mg daily for 7 days. In these three studies, 22/46 (47.8%) of fluconazole-treated patients and 9/22 (40.1%) of placebo-treated patients experienced symptoms consistent with hypoglycemia.

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

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

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

Clinically significant hypoglycemia may be precipitated by the use of fluconazole with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined fluconazole and glyburide use. Fluconazole reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. 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 i.v. for 1 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.

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

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.

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

Zidovudine: Plasma zidovudine concentrations were determined on 2 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 2 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.

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

Drug/Laboratory Test Interactions: None known.

ADVERSE REACTIONS

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

	Percent of Patients with Side Effects	
	Fluconazole (n=448)	Intravaginal Products (n=422)
Drug Related Side Effects	**26.1**	**15.9**
Nausea	6.7	0.7
Abdominal Pain	5.6	1.7
Diarrhea	2.7	0.5
Dyspepsia	1.3	0.2
Headache	12.9	6.6
Application Site Reactions	0.0	4.5
Dizziness	1.3	0.0
Taste Perversion	1.3	0.0

Most of the reported side effects were mild to moderate in severity. Occasional allergic reactions including pruritus and urticaria were reported.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

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

Treatment

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Fluconazole is largely excreted in urine. A 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

Vaginal Candidiasis - Oral

The recommended dosage of fluconazole capsules for vaginal candidiasis is 150 mg as a single oral dose.

There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function.

PHARMACEUTICAL INFORMATION

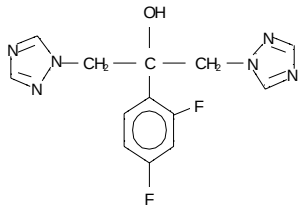
DRUG SUBSTANCE

Common Name: Fluconazole

Chemical Name(s): 1) 1*H*-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1*H*-1,2,4-triazol-1-ylmethyl)-;

2) 2,4-Difluoro-α,α-bis(1*H*-1,2,4-triazol-1-ylmethyl) benzyl alcohol.

Structural Formula:



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

Molecular Weight: 306.28

Description:

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

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

COMPOSITION

NU-FLUCONAZOLE-150 (fluconazole) Capsules, 150 mg, contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose, microcrystalline cellulose, stearic acid.

The capsule shell contains: gelatin, sodium lauryl sulfate, sodium metabisulfite, titanium dioxide.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

NU-FLUCONAZOLE-150 (fluconazole) Capsules are available as hard white opaque gelatin capsules. Each capsule contains 150 mg of fluconazole. Supplied as unit-dose blister packs of 3, 5 and 10 capsules.

INFORMATION FOR THE PATIENT

NU-FLUCONAZOLE-150
(Fluconazole)
Capsules, 150 mg

Oral Treatment for Vaginal Yeast Infections

INDICATION

Your doctor has prescribed NU-FLUCONAZOLE-150 (fluconazole) Capsules for a vaginal yeast (fungal) infection.

NU-FLUCONAZOLE-150 Capsules are used for the treatment of vaginal yeast infection and are taken orally. NU-FLUCONAZOLE-150 Capsules are convenient because one capsule taken by mouth provides a full course of therapy.

HOW TO TAKE NU-FLUCONAZOLE-150 CAPSULES

NU-FLUCONAZOLE-150 Capsules may be taken anytime day or night, with or without meals so you should take the one capsule of NU-FLUCONAZOLE-150 **by mouth immediately** to ensure the earliest possible relief from the infection and its symptoms.

WHEN TO EXPECT RELIEF OF SYMPTOMS

Clearing a yeast infection does take time. Although NU-FLUCONAZOLE-150 Capsules are taken only once, NU-FLUCONAZOLE-150 remains active in your body for several days.

Most patients can expect to see symptom relief begin within 24 hours after taking the capsule. As NU-FLUCONAZOLE-150 works to cure the infection, symptoms will lessen and eventually disappear. If your symptoms have not improved within 3 to 5 days, contact your doctor.

POSSIBLE SIDE EFFECTS OF THIS MEDICATION

In clinical studies of fluconazole capsules, the most common side effects were headache, nausea, abdominal pain, and diarrhea. Most reported side effects were mild to moderate in nature.

Very infrequently, some patients develop skin eruptions or allergy symptoms such as hives after they take this drug. Rarely, severe allergic reactions have occurred.

CAUTIONS

You should not take NU-FLUCONAZOLE-150 Capsules if you ever had an allergic reaction to it or to other antifungal drugs of the same family. If you are in doubt, talk to your doctor or pharmacist.

If you are pregnant, or think you may be pregnant, or if you are nursing, do not take this medication except on the advice of a physician.

If you could become pregnant while taking NU-FLUCONAZOLE-150 Capsules, you should consider using a reliable means of contraception, because the possible effects of this medication on a developing fetus are not known. This is true of many medications.

If you take drugs containing antihistaminic preparations such as terfenadine (Seldane®) or astemizole (Hismanal®), or if you take cisapride (Prepulsid®), consult your doctor before taking NU-FLUCONAZOLE-150 Capsules.

Also inform your doctor if you take oral medicine for diabetes, epilepsy, or if you take blood-thinning medication.

NON-MEDICINAL INGREDIENTS

NU-FLUCONAZOLE-150 Capsules, contain the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose, microcrystalline cellulose, stearic acid; the capsule shell contains gelatin, sodium lauryl sulfate, sodium metabisulfite, titanium dioxide.

STORAGE

Store at room temperature (15-30°C).

If you have any questions, or for more information about NU-FLUCONAZOLE-150 Capsules, and the treatment of vaginal yeast infections, ask your doctor or pharmacist.

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

In Vitro Studies

The clinical relevance of *in vitro* results obtained with azoles is unknown since MIC 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. Flu-conazole 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 1).

Table 1
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

Table 1
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
Cryptococcus neoformans	5	1.25	0.39 - 6.25
Rhodotorula glutinis	1	25	--
Microsporum canis	4	9.4	6.25 - 12.5
Microsporum gypseum	1	50	--
Trichophyton mentagrophytes	21	>100	25 - >100
Trichophyton rubrum	29	39	12.5 - 100
Trichophyton soudanense	2	100	100 - >100
Trichophyton tonsurans	4	42	12.5 - 100
Trichophyton verrucosum	3	37.5	12.5 - 50
Aspergillus flavus	3	>100	>100
Aspergillus fumigatus	7	>100	>100
Aspergillus niger	5	>100	>100
Aspergillus terreus	4	>100	>100

* Values where 3 or more organisms are used are geometric means.
**Defined tissue culture medium consists of Eagles minimal medium with Earle's salts, yeast carbon base and phosphate buffer, pH 7.5, with or without agar.

***In Vivo* Studies**

Vaginal Candidiasis in Predisposed Mice and Rats: A vaginal *C. albicans* infection, induced in mice or ovariectomized rats predisposed with estradiol benzoate, was treated orally with a single dose immediately post-infection (prophylactic) or once daily for 3 days starting 72 hours post-infection (therapeutic). Efficacy was measured as percentage cure compared with untreated controls. In both models in mice or in rats, fluconazole (CD_{50}'s 2.7 and 4.4 mg/kg, respectively, in mice and 2.9 and 2.1 mg/kg, respectively, in rats) was at least 5 to 10 times more effective than ketoconazole (CD_{50}'s 32 and >50 mg/kg, respectively, in mice and 32 and 12.5 mg/ kg, respectively, in rats) in this local infection.

Development of Resistance and Cross-Resistance to Fluconazole: Development of fungal resistance to fluconazole and effects of long-term administration of fluconazole on normal flora have not been systemically 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 muco-cutaneous 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

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 admini-stration, 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 150 mg dose of fluconazole produced a mean C_{max} of 2.70 μg/mL (range: 1.91 to 3.70 μg/mL).

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

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.

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

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

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. Approxi-mately 11% of the radioactivity in urine is due to metabolites. An additional 2% of the total radioactivity is excreted in feces.

The pharmacokinetics of fluconazole do not appear to be affected by age alone but are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function.

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

General

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

In the mouse rotarod test designed to detect sedative and/or skeletal muscle relaxant activity, fluconazole at 5 mg/kg p.o. had no effect 1 hour after administration and produced a slight reduction in performance after 3 hours. It did not affect alcohol sleeping times in mice but significantly pro-longed 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-hydroxy-tryptamine 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 com-ponents 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

Acute Toxicity

Fluconazole had extremely low toxicity when administered orally in single doses to male and female mice and rats; no deaths occurred at doses below 1000 mg/kg in either species. The

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

Subacute and Chronic Toxicity

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

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

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

Carcinogenicity

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

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

Fluconazole, when administered to rodents at high dose levels, is known to affect the biochemical balance of male and female hormones. It has been shown to reduce the levels of several steroids, including the ovarian production of 17-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.

MUTAGENICITY

Ames testing was done with four different strains of Salmonella with and without metabolic activa-tion. 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.

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 labor, and did not impair the development, behaviour or fertility of the offspring. The fetuses from the dams sacrificed on day 20 showed delays in development (an increased incidence of supernumerary ribs at all dose levels and of hydroureters at 20 mg/kg). In the dams allowed to litter, the duration of gestation while remaining within the in-house historical control range, showed a trend towards prolongation in the high dose group. There were no effects on the development, behaviour or fertility of the offspring.

Teratology Studies (Segment II) in Rats: The results of teratology studies conducted in 4 different laboratories were remarkably consistent.

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

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

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

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

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

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

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

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

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 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 [^{3}H]-uridine-labelled *Candida albicans* blastospores by human polymorphonuclear leukocytes (PMNL) *in vitro*. This suggests that fluconazole has little or no influence on the mechanisms involved in microbial killing by PMNL. In contrast, ketoconazole at 10 and 20 μg/mL, significantly reduced (20.9 and 55.9%) the release of [^{3}H]-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 Concanvalin A and Lipopolysaccharide-stimulated mouse spleen lymphocytes as measured by the uptake of [^{3}H]-thymidine. In contrast, ketoconazole at concentrations up to and including 8 μg/mL, significantly reduced the uptake of [^{3}H]-thymidine in the presence of both mitogens.

Effects on Key Endocrine Organs: Fluconazole even at the highest concentration (10 μg/mL), used slightly reduced basal and human chorionic gonadotropin (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-beta 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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