PRODUCT MONOGRAPH

MONICURE™

Fluconazole Capsule 150 mg MONICURE™ COMBO

Fluconazole Capsule 150 mg and Miconazole Nitrate Cream USP 2%

Antifungal Agent

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MONICURE™

Fluconazole Capsule 150 mg

MONICURE™ COMBO

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

	Route of Administration	**Dosage Form/Strength**	**Clinically Relevant Nonmedicinal Ingredients**
MONICURE™	Oral	Capsule, 150 mg	Gelatin, lactose monohydrate. *For a complete listing see Dosage Forms, Composition and Packaging section.*
Monistat DERM™ Cream	Topical	Cream, 2%	Benzoic acid, cetyl alcohol. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

MONICURE™ COMBO contains **MONICURE™ (fluconazole)** and **MONISTAT DERM™ CREAM** (miconazole nitrate). **MONISTAT DERM™ CREAM** (miconazole nitrate) is indicated for the topical treatment of dermatophytes and Candida infections and also lesions caused by mixed infections involving susceptible fungi.

CONTRAINDICATIONS

MONICURE™ (fluconazole) and **MONISTAT DERM™ CREAM** (miconazole nitrate) are contraindicated in patients who have shown hypersensitivity to fluconazole, miconazole nitrate or to any of the excipients used. See the Dosage Forms, Composition and Packaging section of the product monograph for a complete listing of excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used by individuals having hypersensitivity to other azoles when using fluconazole.

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

Co-administration of cisapride* is contraindicated in patients receiving fluconazole (see **WARNINGS AND PRECAUTIONS**).

*not marketed in Canada

WARNINGS AND PRECAUTIONS

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

Clinically significant warnings and precautions for MONICURE™ (fluconazole) and MONISTAT DERM™ CREAM (miconazole nitrate) are listed in alphabetical order.

MONICURE™ (fluconazole)

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 oral 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 **DRUG INTERACTIONS**). The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment may be the result of random variation. While there is evidence that fluconazole can inhibit the metabolism of ethinyl estradiol and levonorgestrel, there is no evidence that fluconazole is a net inducer of ethinyl estradiol or levonorgestrel metabolism. The clinical significance of these effects is presently unknown.

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

Dermatologic
In very rare cases, during the treatment of systemic and vaginal infections, patients have developed exfoliative skin disorders (Stevens - Johnson syndrome, Toxic Epidermal Necrolysis) during treatment with fluconazole.

Hepatic/Biliary/Pancreatic
In the treatment of systemic infections, multiple doses of fluconazole have been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy.

Hypersensitivity
In rare cases, anaphylaxis and angioedema has been reported in patients using fluconazole.

MONISTAT DERM™ CREAM (miconazole nitrate)

Discontinue medication if sensitization or marked irritation (rash, burning, blistering, redness) not present before therapy occur. Avoid introducing MONISTAT DERM™ Cream into the eyes.

Special Populations

MONICURE™ (fluconazole)

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.

Fluconazole should not be used in pregnant women except in patients with severe or potentially life threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus.

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

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

Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies, at 5, 10 and 20 mg/kg and at 5, 25 and 75 mg/kg respectively. Maternal weight gain was impaired at all dose levels, and abortions occurred at 75 mg/kg (approximately 9.4x the maximum recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at the 25 mg/kg dose. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg (approximately 10-40x 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.

Nursing Women:
MONICURE™ is secreted in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

Pediatrics:
MONICURE™ should not be used by girls less than 12 years of age unless advised by a physician.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

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

Percent of Patients with Side Effects

	uconazole (n=448)	ginal 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.		

Less Common Clinical Trial Adverse Drug Reactions
Occasional allergic reactions including pruritus and urticaria were reported.

Post-Market Adverse Drug Reactions
In marketing experience of single dose fluconazole, rare cases of anaphylactic reaction and angioedema have been reported.

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

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

Central and Peripheral Nervous System: seizures.

Dermatologic: alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis (see **WARNINGS AND PRECAUTIONS**).

Gastrointestinal: vomiting.

Hematopoietic and Lymphatic: leukopenia including neutropenia and agranulocytosis, thrombocytopenia.
Immunologic: face edema.

Body as a Whole: face edema, urticaria

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

hypercholesterolemia, hypertriglyceridemia, hypokalemia.

MONISTAT DERM™ CREAM (miconazole nitrate)

On rare occasions it has been reported that patients treated with MONISTAT DERM™ Cream experienced mild pruritus, irritation and burning at the site of application.

DRUG INTERACTIONS

Overview

Drug-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 psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy, such as midazolam or triazolam, is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage.

CIMETIDINE
Absorption of orally administered fluconazole does not appear to be affected by gastric pH.

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

COUMARIN-TYPE ANTICOAGULANTS

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

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

Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin- type anticoagulants.

CYCLOSPORINE

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

DRUGS PROLONGING THE QTc INTERVAL

The use of fluconazole in patients concurrently taking drugs metabolized by the Cytochrome P- 450 system may be associated with elevations in the serum levels of these drugs.

Astemizole*: 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 torsade de pointes in patients to whom fluconazole and cisapride were coadministered. 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 60 mg BID for 15 days. Fluconazole 200 mg was administered daily from days 9 through 15. Fluconazole did not affect terfenadine plasma concentrations. Terfenadine acid metabolite AUC increased 36% ± 36% (range: 7 to 102%) from day 8 to day 15 with the concomitant administration of fluconazole. There was no change in cardiac repolarization as measured by Holter QTc intervals. However, another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. Therefore the combined use of fluconazole at doses of 400 mg or higher with terfenadine is contraindicated (see **CONTRAINDICATIONS**). Patients should be carefully monitored if they are being

*not marketed in Canada
concurrently prescribed fluconazole at multiple doses lower than 400 mg/day with terfenadine.

HYDROCHLOROTHIAZIDE
Concomitant oral administration of 100 mg fluconazole and 50 mg hydro-chlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and C_{max} compared to fluconazole given alone. There was a mean ± SD increase in fluconazole AUC and Cmax 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
Oral contraceptives were administered as a single dose both before and after the oral administration of fluconazole 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of fluconazole. The mean increase in ethinyl estradiol AUC was 6% (range: -47 to 108%) and levonorgestrel AUC increased 17% (range: -33 to 141%).

Twenty-five normal females received daily doses of both 200 mg fluconazole or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving fluconazole during one cycle and placebo during the other. The order of study treatment was random. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (day 10) of both cycles. Following administration of 200 mg of fluconazole, the mean percentage increase of AUC for levonorgestrel compared to placebo was 25% (range: -12 to 82%) and the mean percentage increase for ethinyl estradiol compared to placebo was 38% (range: -11 to 101%). Both of these increases were statistically significantly different from placebo.

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

symptoms consistent with hypoglycemia.

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

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

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

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

PHENYTOIN
Fluconazole increases the plasma concentrations of phenytoin. Phenytoin AUC was determined after 4 days of phenytoin dosing (200 mg daily, orally for 3 days, followed by 250 mg intravenously for one dose) both with and without the administration of fluconazole (oral fluconazole 200 mg daily for 16 days) in 10 normal male volunteers. 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.

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

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

Rifampin enhances the metabolism of concurrently administered fluconazole.

TACROLIMUS
There have been reports that an interaction exists when fluconazole is administered

concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were coadministered.

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

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

Drugs exhibiting no significant pharmacokinetic interactions with fluconazole:

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

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

Drug-Food Interactions
Interactions with foods have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

MONISTAT DERM™ CREAM (miconazole nitrate)

There are no known drug interactions with topical miconazole nitrate.

DOSAGE AND ADMINISTRATION

MONICURE™ (fluconazole)

Dosing Considerations
The recommended dosage of **MONICURE™** for vaginal candidiasis is 150 mg as a single oral dose.

Recommended Dose and Dosage Adjustment
There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function.

MONISTAT DERM™ CREAM (miconazole nitrate)

Apply sufficient MONISTAT DERM™ CREAM to cover the affected area twice daily, morning and evening. Massage gently until cream disappears. Apply cream as required for external itching as long as symptoms persist.

When used in conjunction with MONICURE™ duration of use should be in accordance with the package instructions on the MONICURE™ COMBO preparation.

Early clinical improvement (1-2 weeks) has been seen in the treatment of infections caused by dermatophytes and Candida species and in mixed fungal infections, but resistant lesions may take longer to clear. Candida infections should be treated for two weeks and dermatophyte infections for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after 30 days of treatment, the diagnosis should be reconsidered.

OVERDOSAGE

MONICURE™ (fluconazole)

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

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

MONISTAT DERM™ CREAM (miconazole nitrate)

Acute overdosage with topical application of MONISTAT DERM™ Cream is unlikely and would not be expected to lead to a life-threatening situation.

MONISTAT DERM™ Cream is intended for external application and not for oral use. In the event of accidental ingestion of this product, contact a doctor or Poison Control Centre at once.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

MONICURE™ (fluconazole)

Mechanism of Action

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

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.

Pharmacokinetics

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

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

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

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

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 fluid: plasma ratios ranging from 0.36 to 0.71 over the first 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 radiolabelled fluconazole, greater than 90% of the radioactivity is excreted in the urine. Approximately 11% of the radioactivity in urine is due to metabolites. An additional 2% of the total radioactivity is excreted in feces.

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

MONISTAT DERM™ CREAM (miconazole nitrate)

Mechanism of Action

Depending upon concentration, miconazole nitrate exhibits broad spectrum in vitro fungistatic or fungicidal activity against species of the genus Candida. Miconazole nitrate also inhibits several other genera of fungi, including dermatophytes and yeasts, as well as gram positive bacteria.

Miconazole nitrate inhibits the biosynthesis of ergosterol or other sterols, damaging the fungal cell wall membrane and altering its permeability. In fungi, it also inhibits biosynthesis of triglycerides and phospholipids as well as oxidative and peroxidative enzymes. The latter action results in intracellular buildup of toxic concentrations of hydrogen peroxide, which may contribute to deterioration of subcellular organelles and cellular necrosis.

Candida albicans cells have been observed to exhibit progressive cytoplasmic deterioration and prominent shape changes resulting in complete cell necrosis depending on the dose and duration of exposure to miconazole nitrate. The sequence of morphologic alterations induced by miconazole nitrate at fungistatic doses (10-6M) are lysis of cytoplasmic organelles, focal to complete loss of cell plasmalemma and irregular thickening of the cell wall containing multiple inclusions. Administration of fungicidal doses (10-4M) induces a completely necrotic cell interior with an unaltered cell wall.

Miconazole nitrate has been clinically effective in treating tinea pedis (athlete's foot), tinea cruris, tinea corporis, and tinea versicolor caused by dermatophytes. MONISTAT DERM™ Cream is also effective in cutaneous candidiasis. Among the organisms against which MONISTAT DERM™ Cream has been found effective are Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton interdigitale, Epidermophyton floccosum, Micosporum canis, Micosporum gypseum, species of Candida including C. albicans, and Maleassezia furfur.

Not all species or strains of a particular organism may be susceptible to miconazole nitrate.

To date, no wild strains or fungal mutants with substantial acquired resistance to miconazole have been reported; however, miconazole resistant Candida albicans has been isolated from an infant following bladder irrigation with miconazole for the treatment of urinary candidiasis.

Pharmacokinetics

The absorption, metabolism and excretion of orally, intravaginally and topically administered labelled miconazole nitrate were observed in healthy normals. Blood, urine and faecal samples were taken. The study indicated that the absorption and excretion of miconazole administered orally were unrelated to dosage and duration of treatment. Although 10-20% of the administered oral dose of radioactivity could be recovered in the urine, less than 1% was due to unchanged miconazole nitrate. A large amount of the 40-55% of administered dose recovered in the feces was unchanged miconazole nitrate. Only about 1% of the administered intravaginal dose of radioactivity was recovered from urine and only 0.14% to 0.67% of the topically administered dose, indicating low absorption from each. Eight hours after topical examination, 90% of the drug was recovered from the skin.

STORAGE AND STABILITY

MONICURE™ (fluconazole)

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

MONISTAT DERM™ CREAM (miconazole nitrate)

MONISTAT DERM™ Cream should be stored at controlled room temperature (15°C - 30°C)

DOSAGE FORMS, COMPOSITION AND PACKAGING

MONICURE™ COMBO is supplied in a box which contains MONICURE™ and MONISTAT DERM™ CREAM.

MONICURE™ (fluconazole) 150 mg capsule is available as a hard, white, opaque, gelatin capsule, imprinted with F150.

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

MONISTAT DERM™ CREAM (miconazole nitrate) is supplied as 2% miconazole nitrate cream in a 9 gram tube.

Composition:
MONICURE™ (fluconazole) 150 mg capsule contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, stearic acid, talc.

The capsule shell contains: gelatin, titanium dioxide.

MONISTAT DERM™ CREAM (miconazole nitrate) is a water miscible, white cream containing 2% miconazole nitrate as the active ingredient. Non-medicinal ingredients: benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

MONICURE™ (fluconazole)

Drug Substance

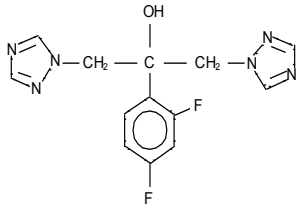
Proper name: Fluconazole

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

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

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

Structural formula:



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

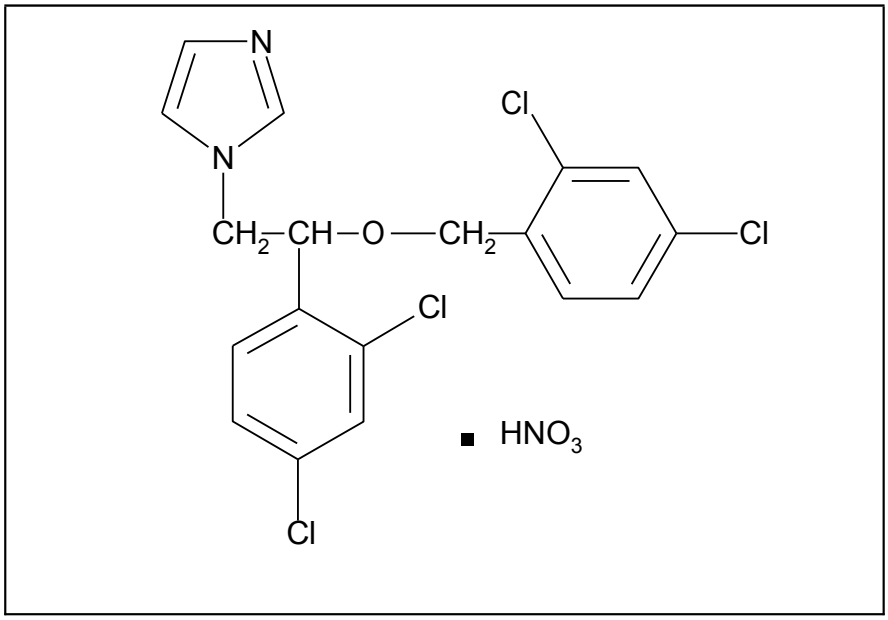
Fluconazole is a very weak base with a pKa of 1.76 at 24°C and as a consequence will be essentially non-protonated at pH values above 3.5. m.p. = 140.3°C. The partition coefficient Log P = +0.5.

MONISTAT DERM™ CREAM (miconazole nitrate)

Drug Substance

Proper Name: Miconazole Nitrate
Name: 1-{2,4-dichloro-ß-[(2,4-dichlorobenzyl)oxy]phenethyl}--imidazole nitrate.

Structural Formula:



Molecular Formula: $C_{18}H_{14}Cl_4N_2O \cdot HNO_3$ Molecular Weight: 479.16

Description: Miconazole nitrate is a white, crystalline or microcrystalline powder, very slightly soluble in water (0.03%) and very slightly to slightly soluble in most common organic solvents and dilute inorganic acids.

CLINICAL TRIALS

MONICURE™ (fluconazole)

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

Study Demographics and Trial Design

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

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

Study results

Reference	Primary Endpoints	alue for fluconazole 150 mg
Adetoro 1990	CC & MC 8 days CC & MC 32 days	87% 87%
Andersen et al. 1989	CC 5 - 16 days CC 27 - 62 days MC 5 - 16 days MC 27 - 62 days	99% 93% 85% 72%
Mendling et al. 2004	MC 14 days MC & CC 14 days	76.0% 59.1%
Mikamo et al 1995	CC 5 - 15 days CC 30 - 60 days MC 5 - 15 days MC 30 - 60 days	80% 76% 76% 70%
Mikamo et al. 1998	CC 5 - 15 days CC 30 - 60 days MC 5 - 15 days MC 30 - 60 days	80% 76% 76% 70%
Multicentre Study Group 1988	CC 5 - 16 days CC 27 - 62 days MC 5 - 16 days MC 27 - 62 days	97% 88% 94% 73%
O-Prasertsawat & Bourlert 1995	CC 7 days CC 28 days MC 7 days MC 28 days	88.7% 69.8% 79.2% 60.4%
Phillips et al. 1990	CC	94.7%
Sobel et al. 1995	CC 14 days CC 35 days MC 14 days MC 35 days	94% 75% 77% 65%
Timonen 1992	CC 7 days MC 7 days MC 30 days	100% 83.3% 72.2%
van Heusden et al. 1990	CC 6 - 10 days CC 22 - 44 days MC 6 - 10 days MC 22 - 44 days	81% 86% 98% 74%
van Heusden et al. 1994	MC 7 days MC 28 days	82% 75%
Wooley & Higgins 1995	CC 7 - 10 days MC 7 - 10 days	62% 83%

CC: clinical cure, MC: mycological cure

Comparative Bioavailability Studies:

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

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

Fluconazole (1 x 150 mg) From measured data **uncorrected potency** Geometric Mean Arithmetic Mean (CV%)

Parameter	**MONICURE™**	**Diflucan 150® † (Pfizer Canada)**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_{0-72h} (µg·hr/mL)	87.2 89.9 (20.4)	89.6 92.3 (20.8)	97.3	94.1 - 101
AUC_{I} (µg·hr/mL)	141.9 147.3 (21.5)	140.8 144.8 (21.8)	100.8	90.6 - 112
C_{max} (µg/mL)	2.26 2.29 (19.1)	2.76 2.76 (15.4)	81.8	75.5 – 88.8
T_{max} (h)*	5.33 (60.4)	1.67 (45.1)		
$t_{1/2}$ (h)*	44.6 (27.4)	42.1 (21.8)		

*Arithmetic means only (CV%).
†Diflucan 150® is manufactured by Pfizer Canada Inc. and was purchased in Canada.

MONISTAT DERM™ CREAM (miconazole nitrate)

Topical administration of MONISTAT miconazole nitrate cream 2% has been effective in the local treatment of fungal infections of the skin and nails, including tinea pedis, tinea cruris, tinea corporis, as well as tinea versicolor. Clinical studies have involved several treatment periods but experience indicates that topical applications should continue for two weeks for tinea cruris, tinea corporis and tinea versicolor and for four weeks for tinea pedis, to lessen the probability of recurrence.

Intravaginal administration of MONISTAT miconazole nitrate 2% for 7 days has been determined to be effective for the treatment of vulvovaginal candidiasis. Clinical experience has indicated that the administration of a small amount of MONISTAT DERM™ CREAM

miconazole nitrate 2% to the vulvar area when an intravaginal solid dosage is being used provides the added benefit of the cream form for particularly severe external symptoms of itching and irritation.

DETAILED PHARMACOLOGY

MONICURE™ (fluconazole)

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

In the mouse rotarod test designed to detect sedative and/or skeletal muscle relaxant activity, fluconazole at 5 mg/kg p.o. had no effect 1 hour after administration and produced a slight reduction in performance after 3 hours. It did not affect alcohol sleeping times in mice but significantly prolonged pentobarbital sleeping time. At concentrations up to 100 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 anaesthetized cat. It produced moderate cardiovascular changes which were transient and returned to pretreatment levels within 10 minutes of administration. In the cat, fluconazole did not display sympathomimetic or ganglion stimulating or blocking activity. Minor alterations in the cardiovascular responses to norepinephrine, isoproterenol, histamine and acetylcholine occurred but were not sufficiently marked or consistent to indicate a direct effect of fluconazole on the receptors for these drugs. Additionally, fluconazole had no anti-5-hydroxytryptamine activity. Somatic function remained essentially normal and respiration was unchanged.

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

MONISTAT DERM™ CREAM (miconazole nitrate)

ANIMAL

1. Tissue and Whole Animal

The agonist activity of miconazole on the guinea pig ileum, rabbit duodenum, rabbit spleen and rat stomach fundus tissue preparations is limited to a slight initial tonus increase observed with the rabbit duodenum preparation at concentrations of 2.5 - 10 mg/l. This compound is observed to antagonize the spasmogenic effects of bradykinin, serotonin, nicotine, eledoisin, angiotensin and histamine, but is devoid of anticholinergic (rabbit duodenum), antiserotoninergic (rat

stomach fundus) anti-"-adrenergic (rabbit spleen) and ß-adrenergic blocking (fowl rectal caecum) activity.

Miconazole given to mice in a single dose of 40 mg/kg had no influence on the licking reflex or other gross behavioural characteristics. In addition, rats treated with this regimen showed no autonomic or CNS induced effects. As well, no morphine-like properties, anticonvulsant effects or change in body temperature was recorded in this species. After repeated administration at this dose level (40 mg/kg/day for 7 consecutive days) no significant changes were again observed in behavioural characteristics and gross overall condition of pathological examination at autopsy.

2. Metabolism and Pharmacokinetics

a) In Vitro

Rats (miconazole nitrate tritium labelled on the 2-ethyl group)
Incubation of tritium-labelled miconazole nitrate was carried out with the 10,000 gm supernatant fractions and microsomal fractions of the liver, lungs and kidneys of the Wistar rat. The major metabolite was "-(2,4-dichloro-phenyl)-1H-imidazole-1-ethanol (R 14821). Whereas more than 70% of the drug was unmetabolized, this metabolite, resulting from an oxidative O - dealkylation by microsomal enzymes, amounted to about 20% of total reactivity. The microsomal enzymes responsible for this metabolic breakdown were twice as active in the liver as in the lungs or the kidneys.

Humans (miconazole nitrate tritium labelled on the 2-ethyl group)
The binding of miconazole nitrate to human plasma proteins, and the distribution of the drug in human blood, blood cell suspension and ghost cell suspension were studied by equilibrium dialysis. Human blood was obtained by venous puncture from health male (8) and female (3) volunteers who had not taken any medication for at least two weeks, from patients (4) with chronic renal failure and from patients (4) who were under haemodialysis treatment.

Miconazole nitrate was found to bind very strongly to human plasma proteins. For example, a 4% HSA solution bound miconazole nitrate for 98% with an overall association constant of 91.6×10^3. Even a 1.5% human gamma globulin solution bound the drug for about 81% with an overall association constant of 8.0×10^3. The binding of miconazole nitrate to the plasma proteins amounted to 98.7%. In blood, 1.2% was distributed in the plasma water, 88.2% was bound to the plasma proteins and 10.6% to the blood cells.

The percentage of bound miconazole was not influenced by the total drug concentration within the tested range from 0.1 to 10.0×10^{-6}M. In a blood cell suspension 97.6% of the drug was bound to the blood cells, probably due to the binding properties of not only the cell membranes but also inner constituents such as haemoglobin.

No significant sex differences and only minor individual differences were found for the plasma protein binding and the distribution of miconazole nitrate in blood. Only very small differences were found between the plasma protein binding and the distribution of the drug in blood or

normal subjects, of patients with chronic renal failure and of patients under haemodialysis treatment.

b) In Vivo

Studies were conducted using miconazole labelled with tritium at C-2 of the imidazole ring or the ß-carbon of the ethyl side chain. It was noted that the tritium label at C-2 of the imidazole ring was labile.

Rats (miconazole tritium labelled at C-2 of the imidazole ring)
Five male Wistar rats were each given an oral dose of 40 mg/kg miconazole in PEG-200. During the four days when urine and faeces were collected, 66% of the total radioactivity administered was recovered; 62% after 48 hours. In the urine collected more than 37% of the radioactivity recovered was in the form of tritiated water. At autopsy (day 4) blood, liver and brain tissues contained 1.9% of the administered radioactivity. Examination of the excreta by the inverse isotope dilution method revealed that 18% of the administered dose was excreted unchanged, 19%, as "-(2,4-dichlorophenyl)-imidazole-1-ethanol or its parent ketone and traces as imidazole.

Dogs and Rabbits (miconazole tritium labelled at C-2 of the imidazole ring)
In separate excretion and absorption studies involving 2 animals per study, miconazole was administered intravaginally in carbowax 1000 and wecobee FS and M (7:3) vehicles to beagle bitches (1 mL of 1% formulation) and New Zealand white rabbit doe (0.5 mL of 1% formulation). In the excretion studies urine and faeces were collected for 12 days from the dogs and urine only from the rabbits. In both species the major percentage of the recovered radioactivity was obtained during the 3 days after dosing. In dogs greater than 60% of the radioactivity was in the urine where the carbowax vehicle was used whereas less than 50% was recovered in the urine of dogs given miconazole in the wecobee vehicle. This observation was made with rabbits as well. In the absorption studies blood samples were obtained at 2, 4, 7 and 25 hours. Peak levels in dogs occurred 4 - 7 hours after dosing whereas in rabbits blood levels peaked at 2 hours. The highest level in dogs (0.06 mg/mL) was found with the carbowax vehicle as was the case with rabbits (0.17 - 0.18 mg/mL). At autopsy (25 hours) the vaginas were dissected and washed. Only 0.08% of the administered dose to dogs and 0.456% to rabbits was found in the tissues and washings.

Rabbits (miconazole tritium labelled in the $-carbon of the ethyl side chain)
Vaginal suppositories (2% miconazole) were administered to 2 New Zealand White rabbits. Urine and faeces were collected daily and blood at 3, 6, 24, 72, 96, 144, and 168 hours. Most of the administered radioactivity (90% in one animal and 70% in the other) was excreted in eight days. Fifty percent of the tritium excreted was recovered in 2-3 days and found in the faeces. Maximum blood levels of tritium occurred 6 hours after dosing (0.95 mg/mL).

MICROBIOLOGY

MONICURE™ (fluconazole)

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

In common with other azole antifungal agents, most fungi show a higher apparent sensitivity to fluconazole *in vivo* than *in vitro*. Both orally and intravenously administered fluconazole was active in a variety of animal fungal infection models. Activity has been demonstrated against opportunistic mycoses, such as infections with *Candida spp*. including systemic candidiasis and in immunocompromised animals; with *Cryptococcus neoformans*, including intracranial infections; with *Aspergillus spp.*, including systemic infections in immunocompromised animals; with *Microsporum spp.*; and with *Trichophyton spp*. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitidis*; with *Coccidioides immitis*; including intracranial infection; and with *Histoplasma capsulatum* in normal and immunosuppressed animals.

***In Vitro* Studies**

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 below).

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

Strains	umber of Isolates	Fluconazole MIC	Range MIC
Candida albicans	159	0.39	0.1 – 1.56
Candida glabrata	3	1.9	1.56 – 3.12
Candida guilliermondii	3	0.62	0.39 – 0.78
Candida krusei	10	>25	>25
Candida parapsilosis	19	1.0	0.39 – 3.1
Candida pseudotropicalis	6	0.19	0.04 – 0.39
Candida tropicalis	16	1.42	0.19 – 3.12
Cryptococcus neoformans	5	1.25	0.39 – 6.25
Rhodotorula glutinis	1	25	-
Microsporum canis	4	9.4	6.25 – 12.5

Microsporum gypseum	1	50	-
Trichophyton mentagrophytes	21	>100	25 - >100
Trichophyton rubrum	29	39	12.5 – 100
Trichophyton soudanense	2	100	100 - >100
Trichophyton tonsurans	4	42	12.5 – 100
Trichophyton verrucosum	3	37.5	12.5 - 50
Aspergillus flavus	3	>100	>100
Aspergillus fumigatus	7	>100	>100
Aspergillus niger	5	>100	>100
Aspergillus terreus	4	>100	>100

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

In Vivo **Studies**

Vaginal Candidosis in Predisposed Mice and Rats:
A vaginal *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 h. post-infection (therapeutic). Efficacy was measured as percentage cure compared with untreated controls. In both models in mice or in rats, fluconazole (CD_{50}'s 2.7 and 4.4 mg/kg, respectively, in mice and 2.9 and 2.1 mg/kg, respectively, in rats) was at least 5 to 10 times more effective than ketoconazole (CD_{50}'s 32 and >50 mg/kg, respectively, in mice and 32 and 12.5 mg/kg, respectively, in rats) in this local infection.

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

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

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

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

MONISTAT DERM™ CREAM (miconazole nitrate)

1. In Vitro Antimicrobial Activity: (see tables 1, 2).

Dermatophytes showed high suceptibility to miconazole nitrate at a concentration of 10 mg/ml. Amongst these were Microsporum canis, M, audouinii, M. gypseum, Trichophyton mentagrophytes, T. rubrum, T. tonsurans, T. verrucosum, T. interdigitale, T. ferrugineum, and T. violaceum, as well as Langeronia soudanensis and Epidermophyton floccosum. In most of the dermatophytes studied, growth was also completely inhibited by a 1mg/ml concentration of miconazole and marked fungistatic activity was still observed in some species at concentrations of 0.1 mg/ml.

Yeasts were also sensitive. High fungistatic effect was observed at concentrations of 10 : g/ml and 100 : g/ml in all species studied except for Rhodotorula sp. and Candida tropicalis.

The fungistatic activity of miconazole nitrate was examined in species of dimorphic fungi, agents of fungal mycetoma, Actinomycetales, Phycomycetes and various other fungi.
Concentrations of 100 : g/ml were generally 100 % effective in preventing growth and at concentrations of 10 : g/ml only a few species were not completely inhibited in their growth.

Sporothrix sp. and Cladosporium also proved susceptible to miconazole whereas Aspergillus sp. and Fusarium were less so.

The active bactericidal (bacteriostatic) concentration of miconazole nitrate against all species tested was 10 : g/ml. Among those tested were Erysipelothrix insidiosa, Staphylococcus hemolyticus, Staphylococcus aureus, Streptococcus pyogenes, Enterococcus, Bacillus subtilis, and Bacillus anthracis.

Bacteriostatic activity was also found against two strains of penicillin-resistant Staphylococcus aureus.

The drug was found devoid of any activity against gram-negative bacteria.

Table 1

Fungal Species	Lowest dose levels of miconazole inhibiting growth of stated fungal species after 14 days incubation (: g/ml)						
	1,000	100	10	1	0.1	0.01	0.001
Trichophyton mentagrophytes	=====	=====	=====	=====	---------		
Epidermophyton floccosum	=====	=====	=====	=====	---------		
Trichophyton ferrugineum	=====	=====	=====				
Trichophyton verrucosum	=====	=====	=====				
Trichophyton rubrum	=====	=====	=====				
Trichophyton violaceum	=====	=====	=====				
Microsporum canis	=====	=====	=====				
Langeronia (T) soudanensis	=====	=====	---------	---------			
Microsporum audouinii	=====	=====	---------				
Trichophyton interdigitale	=====	=====	---------				
Trichophyton tonsurans	=====	=====					
Microsporum gypseum	=====	=====					

===== miconazole complete inhibition
--------- marked inhibition

Table 2

Fungal Species	Lowest dose levels of miconazole inhibition growth of stated fungal species after 14 days incubation (*in vitro*) - : g/ml						
	1,000	100	10	1	0.1	0.01	0.001
Blastomyces brasiliensis* (1)	======	======	======	======	======	======	
Blastomyces dermatitidis (2)	======	======	======	======	======	----------	
Blastomyces dermatitidis (3)	======	======	======	======	======	----------	
Histoplasma capsulatum (1)	======	======	======	======	======		
Blastomyces dermatitidis (4)	======	======	======	======			
Blastomyces dermatitidis (5)	======	======	======				
Madurella mycetomi*	======	======	======	======			
Cephalosporum recifei	======	======	----------				
Allescheria boydii	======	======	----------				
Madurella grisea	======	----------					
Streptomyces madurae*	======	======	======	======			
Streptomyces somaliensis	======	======	======	----------			
Streptomyces pelletierii*	======	======	======				
Nocardia asteroides	======	======	======				
Nocardia brasiliensis	======	======	----------				
Entomophtora coronata	======	======	======				
Basidiobolus meristosporus	======	======	----------				
Saprolegnia sp.	======	======					
Mortierella sp.	---------	---------					
Mucor sp.	---------	---------					
Rhizopus sp.							
Absidia ramosa							
Cladosporium werneckii**	======	======	======	======			
Cladosporium trichoides*	======	======	======	----------			
Sporothrix schenckii	======	======	======				
Phialophora pedrosoi**	======	======	======	----------			
Aureobasidium pullulans	======	======	----------				
Penicillium notatum	======	======					
Alternaria sp.	======	======	----------				
Aspergillus fumigatus	======	======					
Aspergillus niger	======	======					
Aspergillus flavus	======	----------					
Aspergillus nidulans	======	----------					
Geotrichum candidum	======	----------					
Scopulariopsis brevicaulis	---------	---------					
Phialophora verrucosa	---------						
Fusarium sp.	=====						

* score after 4 weeks
** score after 3 weeks
===== complete inhibition
-------- marked inhibition

(1) MP — MP – Mycelial phase
(2) YP/SB — YP – Yeast phase
(3) YP/BHI — BHI - Brain heart infusion broth
(4) MP/SB — SB – Sabouraud broth
(5) MP/BHI

2. In Vivo

Adult guinea pigs pretreated with alloxan (200 mg/kg, i.m.) and infected with Candida albicans received daily topical treatment with 1 g of ointment containing 2% miconazole, nystatin, or amphotericin B, for 14 days starting on the third day after infection.

Miconazole applied topically was effective in curing the lesions induced by C. albicans and was slightly superior to and faster-acting than nystatin and amphotericin B.

Oral doses of miconazole at 160 mg/kg and 40 mg/kg administered for 14 days were effective against Candida albicans-induced lesions. By comparison, oral nystatin and amphotericin B (160 mg/kg) and pimaricin (40 mg/kg) had little effect on the course of the infection.

SUMMARY

Treatment	Dose	# of animals	Route	Lesion scores at 15 days* (no. of animals) 0	1	2	3	4
Controls	excipient	20	topical	0	4	6	7	3
Miconazole	2%	20	topical	1	11	4	3	1
Nystatin	2%	20	topical	0	4	7	7	2
Amphotericin B	2%	20	topical	0	2	4	7	7
Controls	excipient	15	oral	0	1	1	6	7
Miconazole	160 mg/kg	12	oral	10	2	0	0	0
Miconazole	40 mg/kg	14	oral	9	5	0	0	0
Miconazole	10 mg/kg	13	oral	2	2	1	5	3
Nystatin	160 mg/kg	6	oral	0	1	0	2	3
Amphotericin B	160 mg/kg	6	oral	0	0	1	2	3
Rimaricin	40 mg/kg	2	oral	0	0	0	0	2

*NOTE: Inhibition of growth was scored as follows (some spontaneous healing in controls by day 15)

0 = absence of lesions
1 = 1/4 the lesions of infected controls
2 = 1/2 the lesions of infected controls
3 = 3/4 the lesions of infected controls
4 = lesions corresponding to infected controls

Guinea pigs infected with Trichophyton (7 groups) were completely cured following topical treatment with 2% and 0.5% miconazole nitrate. Similar results were obtained for M. canis with 2% miconazole nitrate. Treatment initiated 3 days after infection was different only for M. canis where it proved less effective.

Orally, miconazole nitrate at 160 mg/kg was effective against T. mentagrophytes and six out of seven animals infected with M. canis were completely cured by day 28 (14 days after treatment). Dose of 10 and 40 mg/kg orally were relatively ineffective.

TOXICOLOGY

MONICURE™ (fluconazole)

Acute Toxicity

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

Subacute/Chronic Toxicity

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

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

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

Cardiotoxicity

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

Carcinogenicity

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

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

Fluconazole, when administered to rodents at high dose levels, is known to affect the biochemical balance of male and female hormones. It has been shown to reduce the levels of several steroids, including the ovarian production of 17-β-estradiol in female rats, increase placental weights, reduce uterine weights, and increase testicular weights in rats in chronic studies. The change in the pattern of tumours in this chronic study of fluconazole in rats is an expected consequence of such a hormone imbalance.

Mutagenicity

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

Reproduction and Teratology

General Fertility (Segments I and III) in rats:

Male rats were treated for 80 days prior to and during mating while female rats were treated for 14 days prior to and during pregnancy and lactation. Both sexes were treated orally with 5, 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 foetuses from the dams sacrificed on day 20 p.i. showed delays in development (an increased incidence of supernumerary ribs at all dose levels and of hydroureters at 20 mg/kg). In the dams allowed to litter, the duration of gestation while remaining within the in-house historical control range,

showed a trend towards prolongation in the high dose group. There were no effects on the development, behaviour or fertility of the offspring.

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

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

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

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

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

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

There were no effects on the foetuses at 5 or 25 mg/kg and there were too few foetuses at 75 mg/kg to permit a valid assessment of any drug effect.

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

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

Special Toxicology 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.

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 Defence 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 concanavalin A and Lipopolysaccharide-stimulated mouse spleen lymphocytes as measured by the uptake of [^{3}H]-thymidine. In contrast, ketoconazole at concentrations up to and including 8 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 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 estrogen *in vitro* by rat ovarian microsomes showed that fluconazole was approximately 20-fold less potent than ketoconazole as an inhibitor of rat ovarian aromatase (IC_{50} values 1.4 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*.

MONISTAT DERM™ CREAM (miconazole nitrate)

ANIMAL

1. Acute

Acute oral toxicity of miconazole (7-day mortality) was assessed in male white mice, male Wistar rats, female guinea pigs and male and female mongrel dogs. The compound was administered in a micronized aqueous suspension. The following values were obtained:

Species	LD_{50} (95% Confidence Limits) mg/kg
Mice	578 (324.4 - 1030)
Rats	> 640
Guinea Pigs	276 (201.2 - 378.3)
Dogs	> 160

The intraperitoneal LD_{50} in male Swiss Webster mice was 670 mg/kg $\pm$ 0.36 S.E.

2. Subacute

Rats
Adult Wistar Rats (10 males and 10 females per dose group) were given miconazole at 80, 10 and 5 mg/kg/day in their diet for 13 weeks. All animals survived the test. The urine of treated animals was compared with the urine of control animals. Specific gravity was increased in the high dose group and urine pH was lowered in the intermediate and high dose groups. In addition, minor changes in liver, thymus, spleen and kidney were noted in the high dose group after histopathological examination. From these results the no-effect dose is calculated to be less than 80 mg/kg, but greater than 20 mg/kg.

Dogs
Adult Beagle dogs (3 males and 5 females per dose group) were given miconazole at 40, 20 and 2.5 mg/kg/day orally by capsule, 6 days a week, for 13 weeks. All animals survived the test. The following changes were noted: haematocrit and haemoglobin values were lowered in the high dose group; serum calcium and cholesterol and sulfhydryl values decreased in the intermediate and high dose groups; alkaline phosphatase was elevated in the high dose group and the odd animal in the high dose group salivated and would vomit subsequent to drug administration. At autopsy slight liver changes were noted in the high dose group animals.
From these results the no-effect dose is calculated to be less than 40 mg/kg but greater than 10 mg/kg.

3. Chronic

Rats
Adult Wistar rats (30 males and 30 females per dose group) were given miconazole at 160, 40 and 10 mg/kg/day in their diet. Interim sacrifices of 20 animals (10 males and 10 females) per dose level were made at 6 and 12 months, the remaining animals being sacrificed at the termination of the study (18 months). Histopathology showed some slight liver changes which appeared to be more pronounced in the males. However, this finding did not progress with time. No other significant findings were reported and miconazole was well tolerated up to 160 mg/kg over the study period.

Dogs
Adult Beagle dogs (3 males and 3 females per dose group) were given oral doses by capsule of miconazole at 20, 5 and 1.25 mg/kg/day, 6 days a week for 52 weeks. All animals survived the study period. Persistent increased alkaline phosphatase levels and slightly increased SGPT values were noted with the high dose group; however, all other measured parameters were normal. At autopsy no significant histopathological changes were evident.

4. Reproductive Studies

Fertility in Rats

Adult Wistar rats (2 groups per dose level) were given miconazole at 320, 160 and 80 mg/kg in their diet as follows:

Group A: 20 males - drug given 60 days premating 20 females - no drug

Group B: 20 males - no drug
20 females - drug 14 days premating plus 21 days gestation

Females were sacrificed at day 22 of gestation. There was no difference between dose levels or groups A or B in pregnancy rate, but the number of dead foetuses and resorbed foetuses was increased in the high dose level. No abnormalities were noted among pups born to dosed females with the exception of two animals with rib deformities born to a high dose female.
Based on the study findings, miconazole had no effect on the fertility of dosed males or females.

Peri-and Postnatal Studies in Rats

In one study, pregnant rats (20 animals per dose group) were given miconazole at 320, 160 and 80 mg/kg in their diet from day 16 of gestation through the 3 week lactation period. The gestation period was increased one day for the intermediate and high dose groups. In the test animals, litter size and the number of live foetuses at birth were slightly lower when compared to controls. In addition, body weight gains in the intermediate and high dose groups for the surviving pups were lower, whereas the birth weights of pups in the various groups had not differed.

In a second study pregnant Long-Evans derived rats (20 animals per dose group) were given miconazole, suspended in carboxymethylcellulose at 80, 40 and 20 mg/kg by gastric gavage from day 14 of gestation through to day 21 post partum. In the high dose group a prolonged gestation period associated with an increase in the number of still born pups was noted.
Performance of the other dose groups was comparable to controls.

5. Teratology

Rats

Pregnant rats (20 animals per dose group) were given miconazole at 160 and 80 mg/kg in their diet from day 6 to day 15 of gestation. On day 22 of gestation, foetuses were delivered by caesarean section. No abnormalities were noted in this study either in the offspring or the reproductive performance of the dams.

Rabbits

Pregnant New Zealand white rabbits were given miconazole in carboxymethylcellulose at 80 (17 animals), 40 (15 animals) and 20 (15 animals) mg/kg by gavage from day 7 to day 19 of gestation. On day 30 of gestation, the animals were sacrificed. No adverse effect was noted at the low or intermediate dose levels upon maternal mortality, pregnancy rate or early parturition or on foetal resorption, size, sex ratio or malformation. At the high dose level there was evidence of maternal and foetal toxicity as indicated by maternal weight loss during gestation,

lengthened period of gestation and significant foetal resorption. However, at the high dose there was no indication of teratogenicity.

6. Other Studies

Intravaginal irritation studies have been carried out in rabbits for periods ranging from 10 days to 3 months. Miconazole in its cream formulation (2%) and placebo cream were installed daily at a dosage of 1 gm of cream formulation (5-7 mg/kg of miconazole). Under the experimental conditions the cream base with or without miconazole showed a low order of irritation to the intact vaginal mucosa. No evidence of systemic toxicity was noted. Similar findings were reported for vaginal irritation studies with rabbits and monkeys (3 months) utilizing 1g carbowax suppositories containing miconazole (2%).

Dermal and occular studies on rabbits ranging from 24 hours to 1 month in duration have revealed little irritation when miconazole was utilized in the 2% cream formulation. Dose levels of miconazole in these studies were as high as 50 mg/kg/day. In addition no evidence of systemic toxicity has been apparent in these studies.

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PART III: CONSUMER INFORMATION

MONICURE™
Fluconazole Capsule 150 mg

This leaflet is part III of a three-part "Product Monograph" published when MONICURE™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MONICURE™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

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

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

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

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

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

What it does:
MONICURE™ is an antifungal medication. The active ingredient fluconazole works by stopping the growth of the fungi that cause vaginal yeast infections.

When it should not be used: Do not use if you are:
- pregnant
- trying to become pregnant
- nursing
- allergic to fluconazole, related azoles (e.g. clotrimazole / miconazole) or other ingredients in the product
- taking allergy drugs (e.g. astemizole* / terfenadine*)
- taking cisapride*

*not marketed in Canada

What the medicinal ingredient is: Fluconazole

What the important nonmedicinal ingredients are: Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, stearic acid, talc. Capsule shell contains: gelatin, titanium dioxide.

What dosage forms it comes in:
MONICURE™ is available in a capsule containing 150 mg (white) fluconazole.

WARNINGS AND PRECAUTIONS

BEFORE you use MONICURE™ talk to your doctor or pharmacist if:

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

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

Yeast infections do not cause:
- Fever

- Chills
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Pain upon urination
- Unexplained pain in your lower back or either shoulder
- Foul-smelling discharge

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

INTERACTIONS WITH THIS MEDICATION

BEFORE you use MONICURE™ talk to your doctor or pharmacist if you are taking any other drug especially drugs for:

- AIDS/HIV (zidovudine)
- Allergies (Astemizole*, Terfenadine*)
- Asthma (theophylline)
- Antibiotics (rifabutin, rifampicin)
- Blood Thinners (warfarin)
- Diabetes (glyburide, glipizide, tolbutamide)
- Diuretics (hydrochlorothiazide)
- Epilepsy (phenytoin)
- Immune System suppression (cyclosporine, tacrolimus)
- Stomach (cimetidine, cisapride*)
- Sedation (midazolam, triazolam)

* not marketed in Canada

PROPER USE OF THIS MEDICATION

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

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

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

Overdose:

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects in clinical studies were headache, nausea, abdominal pain, and diarrhea. Most reported side effects were mild to moderate in nature.

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

Stop use and contact a doctor or pharmacist if you:
develop skin eruptions, experience new rash or irritations or allergy symptoms such as hives. Rarely, severe allergic reactions (swelling of face, eyes, mouth, hands and feet) have occurred.

HOW TO STORE IT

Store MONICURE™ at room temperature (15 – 30 °C). Keep out of reach of children.

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

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

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

In case of accidental overdose call a doctor or poison control centre immediately, even if there are no symptoms.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting Insight Pharmaceuticals, LLC at 1-800-891-4857.

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PART III: CONSUMER INFORMATION

MONICURE™ COMBO

MONICURE™
Fluconazole Capsule 150 mg

MONISTAT DERM™ CREAM
Miconazole Nitrate Cream USP 2%

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ABOUT THIS MEDICATION

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

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

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

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

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

What it does:
MONICURE™ COMBO is an antifungal medication containing two products. MONICURE™ is an antifungal medication. The active ingredient fluconazole works by stopping the growth of the fungi that cause vaginal yeast infections. MONISTAT DERM™ CREAM which contains miconazole nitrate works by relieving the external irritation associated with yeast infection.

When it should not be used: Do not use if you are:
- pregnant
- trying to become pregnant
- nursing
- allergic to fluconazole, miconazole nitrate, related azoles (e.g. clotrimazole) or other ingredients in the product
- taking allergy drugs (e.g. astemizole* / terfenadine*)
- taking cisapride*

*not marketed in Canada

What the medicinal ingredient is: Fluconazole 150 mg (Oral Capsule) Miconazole nitrate USP 2% (Cream)

What the important nonmedicinal ingredients are:
Oral capsule: Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, stearic acid, talc. Capsule shell contains: gelatin, titanium dioxide.

External Cream: benzoic acid, cetyl alcohol, isopropyl myristate, polysorbate 60, potassium hydroxide, propylene glycol, purified water, stearyl alcohol.

What dosage forms it comes in:
MONICURE™ is available in a capsule containing 150 mg (white) fluconazole.
MONISTAT DERM™ CREAM is available in a 9 g tube containing 2% miconazole nitrate.

WARNINGS AND PRECAUTIONS

BEFORE you use MONICURE™ COMBO talk to your doctor or pharmacist if:

- you are having your first yeast infection
- you have frequent vaginal infections

- you are at increased risk for sexually transmitted diseases, have multiple sexual partners or change partners often
- you have heart disease
- using in children less than 12 years old

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

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

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

Discontinue MONISTAT DERM™ CREAM if sensitization or marked irritation (rash, burning, blistering, redness) not present before therapy occur. Avoid introducing MONISTAT DERM™ CREAM into the eyes.

INTERACTIONS WITH THIS MEDICATION

BEFORE you use MONICURE™ talk to your doctor or pharmacist if you are taking any other drug especially drugs for:

- AIDS/HIV (zidovudine)
- Allergies (Astemizole*, Terfenadine*)
- Asthma (theophylline)
- Antibiotics (rifabutin, rifampicin)
- Blood Thinners (warfarin)
- Diabetes (glyburide, glipizide, tolbutamide)
- Diuretics (hydrochlorothiazide)
- Epilepsy (phenytoin)
- Immune System suppression (cyclosporine, tacrolimus)
- Stomach (cimetidine, cisapride*)
- Sedation (midazolam, triazolam)

* not marketed in Canada

PROPER USE OF THIS MEDICATION

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

MONICURE™

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

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

MONISTAT DERM™ CREAM

Apply a thin layer of cream to the itchy or irritated genital area in the evening and morning as needed. Massage gently until the cream disappears.

Overdose:

In case of accidental overdose call a doctor or poison control centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects in clinical studies were headache, nausea, abdominal pain, and diarrhea. Most reported side effects were mild to moderate in nature. On rare occasions it has been reported that patients treated with MONISTAT DERM™ CREAM experienced mild pruritus, irritation and burning at the site of application.

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

Stop use and contact a doctor or pharmacist if you:
develop skin eruptions, experience new rash or irritations or allergy symptoms such as hives. Rarely, severe allergic reactions (swelling of face, eyes, mouth, hands and feet) have occurred.

HOW TO STORE IT

Store at room temperature (15 – 30 °C). Keep out of reach of children.

Usual dose:

IMPORTANT: PLEASE READ

REPORTING SIDE EFFECTS

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

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhpmps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

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

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting
Insight Pharmaceuticals, LLC at 1-800-891-4857.
This leaflet was prepared by Insight Pharmaceuticals, LLC.

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