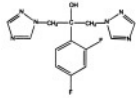


Fluconazole Injection in INTRAVIA Plastic Container

DESCRIPTION

Fluconazole, a member of a new subclass of synthetic triazole antifungal agents, is available as a sterile solution for intravenous use in INTRAVIA plastic container.

Fluconazole is designated chemically as 2,4-difluoro- α,α' -bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol with a molecular formula of C₁₃H₁₂F₂N₆O and molecular weight 306.3. The structural formula is:



Fluconazole is a white crystalline solid which is slightly soluble in water and saline.

Fluconazole injection is an iso-osmotic, sterile, nonpyrogenic solution in a sodium chloride diluent. Each mL contains 2 mg of fluconazole and 9 mg of sodium chloride. Osmolarity is 315 mOsmol/L (calc). The pH is 5.5 (4.0 to 8.0). Injection volumes of 100 mL and 200 mL are packaged in INTRAVIA plastic containers.

The flexible container is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. The flexible container has a foil overwrap. Water can permeate the plastic into the overwrap, but the amount is insufficient to significantly affect the premixed solution.

CLINICAL PHARMACOLOGY

Mode of Action

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

Pharmacokinetics and Metabolism

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Bioequivalence was established between the 100 mg tablet and both suspension strengths when administered as a single 200 mg dose.

Peak plasma concentrations (C_{max}) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20 to 50 hours) after oral administration.

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

Steady-state concentrations are reached within 5 to 10 days following oral doses of 50 to 400 mg given once daily. Administration of a loading dose (on day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11 to 12%). Following either single- or multiple-oral doses for up to 14 days, fluconazole penetrates into all body fluids studied (see table below). In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations regardless of dose, route, or duration of dosing. In patients with bronchiectasis, sputum concentrations of fluconazole following a single 150 mg oral dose were equal to plasma concentrations at both 4 and 24 hours post dose. In patients with fungal meningitis, fluconazole concentrations in the CSF are approximately 80% of the corresponding plasma concentrations.

Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*

Tissue or Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*
Cerebrospinal fluid†	0.5 to 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2

*Relative to concurrent concentrations in plasma in subjects with normal renal function.
†Independent of degree of meningeal inflammation.

In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of fluconazole may need to be reduced in patients with impaired renal function. (See **DOSE AND ADMINISTRATION**.) A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

In normal volunteers, fluconazole administration (doses ranging from 200 mg to 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the ACTH-stimulated cortisol response.

Pharmacokinetics in Children

In children, the following pharmacokinetic data (Mean(%cv)) have been reported:

Age Studied	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (Hours)	C _{max} (mcg/mL)	V _{dss} (L/kg)
9 Months to 13 years	Single-Oral 2 mg/kg	0.40 (38%) N=14	25.0	2.9 (22%) N=16	—
9 Months to 13 years	Single-Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N=15	—
5 to 15 years	Multiple IV 2 mg/kg	0.49 (40%) N=4	17.4	5.5 (25%) N=5	0.722 (36%) N=4
5 to 15 years	Multiple IV 4 mg/kg	0.59 (64%) N=5	15.2	11.4 (44%) N=6	0.729 (33%) N=5
5 to 15 years	Multiple IV 8 mg/kg	0.66 (31%) N=7	17.6	14.1 (22%) N=8	1.069 (37%) N=7

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

In premature newborns (gestational age 26 to 29 weeks), the mean (%cv) clearance within 36 hours of birth was 0.180 (35%, N=7) mL/min/kg, which increased with time to a mean of 0.218 (31%, N=9) mL/min/kg six days later and 0.333 (56%, N=4) mL/min/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later.

Drug Interaction Studies

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

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

Cimetidine: 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 and C_{max}. There was a mean \pm SD decrease in fluconazole AUC of 13% \pm 11% (range: -3.4 to -31%) and C_{max} decreased 19% \pm 14% (range: -5 to -40%). However, the administration of cimetidine 600 mg to 900 mg intravenously over a four-hour period (from one hour before to 3 hours after a single oral dose of fluconazole 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in 24 healthy male volunteers.

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

Hydrochlorothiazide: Concomitant oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and C_{max} compared to fluconazole given alone. There was a mean \pm SD increase in fluconazole AUC and C_{max} of 45% \pm 31% (range: 19 to 114%) and 43% \pm 31% (range: 19 to 122%), respectively. These changes are attributed to a mean \pm SD reduction in renal clearance of 30% \pm 12% (range: -10 to -50%).

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

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

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 \pm SD increase in phenytoin AUC was 88% \pm 68% (range: 16 to 247%). The absolute magnitude of this interaction is unknown because of the intrinsically nonlinear disposition of phenytoin. (See **PRECAUTIONS**.)

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 \pm SD increase in AUC was 92% \pm 43% (range: 18 to 147%). The C_{max} increased 60% \pm 48% (range: -5 to 133%). The C_{min} increased 157% \pm 96% (range: 33 to 360%). The apparent oral clearance decreased 45% \pm 15% (range: -15 to -60%). (See **PRECAUTIONS**.)

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

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

Terfenadine: Six 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% \pm 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. 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. (See **CONTRAINDICATIONS** and **PRECAUTIONS**.)

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. (See **PRECAUTIONS**.)

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

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

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

Rifabutin: There have been published reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. (See **PRECAUTIONS**.)

Tacrolimus: There have been published reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. (See **PRECAUTIONS**.)

Cisapride: A preliminary report from a placebo-controlled, randomized multiple-dose study in subjects given fluconazole 200 mg daily and cisapride 20 mg four times daily starting after 7 days of fluconazole dosing found that fluconazole significantly increased the AUC and C_{max} of cisapride both after single (AUC 102% and C_{max} 92% increases) and multiple (AUC 192% and C_{max} 153% increases) dosing of cisapride.

Fluconazole significantly increased the QTc interval in subjects receiving cisapride 20 mg four times daily for 5 days. (See **CONTRAINDICATIONS** and **PRECAUTIONS**.)

Microbiology

Fluconazole exhibits *in vitro* activity against *Cryptococcus neoformans* and *Candida* spp. Fungistatic activity has also been demonstrated in normal and immunocompromised animal models for systemic and intracranial fungal infections due to *Cryptococcus neoformans* and for systemic infections due to *Candida albicans*.

In common with other azole antifungal agents, most fungi show a higher apparent sensitivity to fluconazole *in vivo* than *in vitro*. Fluconazole administered orally and/or intravenously was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Activity has been demonstrated against fungal infections caused by *Aspergillus flavus* and *Aspergillus fumigatus* in normal mice. Fluconazole has also been shown to be active in animal models of endemic mycoses, including one model of *Blastomyces dermatitidis* pulmonary infections in normal mice; one model of *Coccidioides immitis* intracranial infections in normal mice; and several models of *Histoplasma capsulatum* pulmonary infection in normal and immunosuppressed mice. The clinical significance of results obtained in these studies is unknown.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cr. neoformans*, and antagonism of the two drugs in systemic infection with *Asp. fumigatus*. The clinical significance of results obtained in these studies is unknown.

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

INDICATIONS AND USAGE

Fluconazole injection is indicated for the treatment of:

1. Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, fluconazole was also effective for the treatment of *Candida* urinary tract infections, peritonitis, and systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia.

2. Cryptococcal meningitis. Before prescribing fluconazole for AIDS patients with cryptococcal meningitis, please see **CLINICAL STUDIES** section. Studies comparing fluconazole to amphotericin B in non-HIV infected patients have not been conducted.

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

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

CLINICAL STUDIES

Cryptococcal meningitis: In a multicenter study comparing fluconazole (200 mg/day) to amphotericin B (0.3 mg/kg/day) for treatment of cryptococcal meningitis in patients with AIDS, a multivariate analysis revealed three pretreatment factors that predicted death during the course of therapy: abnormal mental status, cerebrospinal fluid cryptococcal antigen titer greater than 1:1024, and cerebrospinal fluid white blood cell count of less than 20 cells/mm³. Mortality among high risk patients was 33% and 40% for amphotericin B and fluconazole patients, respectively (p=0.58), with overall deaths 14% (9 of 63 subjects) and 18% (24 of 131 subjects) for the 2 arms of the study (p=0.48). Optimal doses and regimens for patients with acute cryptococcal meningitis and at high risk for treatment failure remain to be determined. (Saag, *et al.* N Engl J Med 1992; 326:83-9.)

Pediatric Studies

Oropharyngeal candidiasis: An open-label, comparative study of the efficacy and safety of fluconazole (2 to 3 mg/kg/day) and oral nystatin (400,000 I.U. 4 times daily) in immunocompromised children with oropharyngeal candidiasis was conducted. Clinical and mycological response rates were higher in the children treated with fluconazole.

Clinical cure at the end of treatment was reported for 86% of fluconazole treated patients compared to 46% of nystatin treated patients. Mycologically, 76% of fluconazole treated patients had the infecting organism eradicated compared to 11% for nystatin treated patients.

	Fluconazole	Nystatin
Enrolled	96	90
Clinical Cure	76/88 (86%)	36/78 (46%)
Mycological eradication*	55/72 (76%)	6/54 (11%)

* Subjects without follow-up cultures for any reason were considered nonevaluable for mycological response.

The proportion of patients with clinical relapse 2 weeks after the end of treatment was 14% for subjects receiving fluconazole and 16% for subjects receiving nystatin. At 4 weeks after the end of treatment the percentages of patients with clinical relapse were 22% for fluconazole and 23% for nystatin.

CONTRAINDICATIONS

Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles. Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study. Coadministration of cisapride is contraindicated in patients receiving fluconazole. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies** and **PRECAUTIONS**.)

WARNINGS

(1) Hepatic injury: Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole.

(2) Anaphylaxis: In rare cases, anaphylaxis has been reported.

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

PRECAUTIONS

Drug Interactions: (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies** and **CONTRAINDICATIONS**.) Clinically or potentially significant drug interactions between fluconazole and the following agents/classes have been observed. These are described in greater detail below.

Oral hypoglycemics	Rifampin	Astemizole
Coumarin-type anticoagulants	Theophylline	Rifabutin
Phenytoin	Terfenadine	Tacrolimus
Cyclosporine	Cisapride	

Oral hypoglycemics: Clinically significant hypoglycemia may be precipitated by the use of fluconazole with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined fluconazole and glyburide use. Fluconazole reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When fluconazole is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Coumarin-type anticoagulants: Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Phenytoin: Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Cyclosporine: Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving fluconazole and cyclosporine. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Rifampin: Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of fluconazole when it is administered with rifampin. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Theophylline: Fluconazole increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving fluconazole and theophylline is recommended. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

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. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. 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. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.) The coadministration of fluconazole at doses lower than 400 mg/day with terfenadine 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. The combined use of fluconazole with cisapride is contraindicated. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Astemizole: The use of fluconazole in patients concurrently taking astemizole or other drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when coadministering fluconazole. Patients should be carefully monitored.

Rifabutin: There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Tacrolimus: There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were coadministered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.)

Fluconazole tablets coadministered 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. (See **CLINICAL PHARMACOLOGY: Drug Interaction Studies**.) The data presently available indicate that the decreases in some individual ethinyl estradiol and levonorgestrel AUC values with fluconazole treatment are likely 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.

Physicians should be aware that interaction studies with medications other than those listed in the **CLINICAL PHARMACOLOGY** section have not been conducted, but such interactions may occur.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day (approximately 2 to 7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S. typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 mcg/mL) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5 to 15 times the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See **CLINICAL PHARMACOLOGY**.)

Pregnancy

Teratogenic Effects. Pregnancy Category C: 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 20 to 60 times the recommended human dose); no adverse fetal effects were detected. In several studies in which pregnant rats were treated orally with fluconazole during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20 to 60 times the recommended human dose) to 320 mg/kg 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.

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 to 800 mg/day) fluconazole therapy for coccidioidomycosis (an unindicated use). The relationship between fluconazole use and these events is unclear. Fluconazole should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.

Nursing Mothers

Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of fluconazole in nursing mothers is not recommended.

Pediatric Use

An open-label, randomized, controlled trial has shown fluconazole to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age. (See **CLINICAL STUDIES**.)

The use of fluconazole in children with cryptococcal meningitis, *Candida* esophagitis, or systemic *Candida* infections is supported by the efficacy shown for these indications in adults and by the results from several small noncomparative pediatric clinical studies. In addition, pharmacokinetic studies in children (see **CLINICAL PHARMACOLOGY**) have established a dose proportionality between children and adults. (See **DOSAGE AND ADMINISTRATION**.)

In a noncomparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of fluconazole was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 13/15 (87%) of evaluable patients had a mycologic cure at the end of treatment but two of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

The efficacy of fluconazole for the suppression of cryptococcal meningitis was successful in 4 of 5 children treated in a compassionate-use study of fluconazole for the treatment of life-threatening or serious mycosis. There is no information regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children.

The safety profile of fluconazole in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1,616 days. (See **ADVERSE REACTIONS**.)

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

ADVERSE REACTIONS

In Patients Receiving Multiple Doses for Infections:

Sixteen percent of over 4000 patients treated with fluconazole in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

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

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving fluconazole for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

The following adverse events have occurred under conditions where a causal association is probable:

Hepatobiliary: In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with fluconazole. (See **WARNINGS**.) The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of fluconazole.

In two comparative trials evaluating the efficacy of fluconazole for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Immunologic: In rare cases, anaphylaxis has been reported.

The following adverse events have occurred under conditions where a causal association is uncertain:

Central Nervous System: Seizures.

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

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

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Adverse Reactions in Children:

In Phase I/III clinical trials conducted in the United States and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with fluconazole at doses up to 15 mg/kg/day for up to 1,616 days. Thirteen percent of children experienced treatment related adverse events. The most commonly reported events were vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Treatment was discontinued in 2.3% of patients due to adverse clinical events and in 1.4% of patients due to laboratory test abnormalities. The majority of treatment-related laboratory abnormalities were elevations of transaminases or alkaline phosphatase.

Percentage of Patients With Treatment-Related Side Effects

	Fluconazole (N=577)	Comparative Agents (N=451)
With any side effect	13.0	9.3
Vomiting	5.4	5.1
Abdominal pain	2.8	1.6
Nausea	2.3	1.6
Diarrhea	2.1	2.2

OVERDOSAGE

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

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted.

Fluconazole is largely excreted in urine. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

In mice and rats receiving very high doses of fluconazole, clinical effects in both species included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex and cyanosis; death was sometimes preceded by clonic convulsions.

DOSE AND ADMINISTRATION

Dosage and Administration in Adults:

SINCE ORAL ABSORPTION IS RAPID AND ALMOST COMPLETE, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL AND INTRAVENOUS ADMINISTRATION. In general, a loading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy.

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

Oropharyngeal candidiasis: The recommended dosage of fluconazole for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of oropharyngeal candidiasis generally resolves within several days, but treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

Esophageal candidiasis: The recommended dosage of fluconazole for esophageal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.

Systemic Candida infections: For systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used.

Urinary tract infections and peritonitis: For the treatment of *Candida* urinary tract infections and peritonitis, daily doses of 50 to 200 mg have been used in open, noncomparative studies of small numbers of patients.

Cryptococcal meningitis: The recommended dosage for treatment of acute cryptococcal meningitis is 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after the cerebrospinal fluid becomes culture negative. The recommended dosage of fluconazole for suppression of relapse of cryptococcal meningitis in patients with AIDS is 200 mg once daily.

Prophylaxis in patients undergoing bone marrow transplantation: The recommended fluconazole daily dosage for the prevention of candidiasis of patients undergoing bone marrow transplantation is 400 mg,

once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils per cu mm) should start fluconazole prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per cu mm.

Dosage and Administration in Children:

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

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

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

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. (See **CLINICAL PHARMACOLOGY**.) Based on the prolonged half-life seen in premature newborns (gestational age 26 to 29 weeks), these children, in the first two weeks of life, should receive the same dosage (mg/kg) as in older children, but administered every 72 hours. After the first two weeks, these children should be dosed once daily. No information regarding fluconazole pharmacokinetics in full-term newborns is available.

Oropharyngeal candidiasis: The recommended dosage of fluconazole for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.

Esophageal candidiasis: For the treatment of esophageal candidiasis, the recommended dosage of fluconazole in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/day may be used based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least 2 weeks following the resolution of symptoms.

Systemic Candida infections: For the treatment of candidemia and disseminated *Candida* infections, daily doses of 6 to 12 mg/kg/day have been used in an open, noncomparative study of a small number of children.

Cryptococcal meningitis: For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of 12 mg/kg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of fluconazole is 6 mg/kg once daily.

Dosage in Patients With Impaired Renal Function:

Fluconazole is cleared primarily by renal excretion as unchanged drug. There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function. In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50 to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance (mL/min)	Percent of Recommended Dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.

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

$$\text{Males: } \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females: } 0.85 \times \text{above value}$$

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

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

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

Administration

Fluconazole is administered by intravenous infusion. Fluconazole injection has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of fluconazole should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion.

Fluconazole injection in INTRAVIA plastic containers is intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if the solution is cloudy or precipitated or if the seal is not intact.

Directions for IV Use of fluconazole in INTRAVIA Plastic Containers

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

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

To Open

Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. After removing overwrap, check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

DO NOT ADD SUPPLEMENTARY MEDICATION.

Preparation for Administration:

- Suspend container from eyelet support.
- Remove plastic protector from outlet port at bottom of container.
- Attach administration set. Refer to complete directions accompanying set.

HOW SUPPLIED

Fluconazole Injections: Fluconazole injections for intravenous infusion administration are formulated as sterile iso-osmotic solutions containing 2 mg/mL of fluconazole. They are supplied in INTRAVIA plastic containers containing volumes of 100 mL or 200 mL affording doses of 200 mg and 400 mg of fluconazole, respectively.

Fluconazole Injections in INTRAVIA Plastic Containers:

2J1446 NDC 0338-6046-48 Fluconazole in Iso-osmotic Sodium Chloride Diluent 200 mg/100 mL x 10

2J1445 NDC 0338-6045-37 Fluconazole in Iso-osmotic Sodium Chloride Diluent 400 mg/200 mL x 10

Storage: Store between 77°F (25°C) and 41°F (5°C). Brief exposure up to 104°F (40°C) does not adversely affect the product. Protect from freezing. Avoid excessive heat.

Baxter Healthcare Corporation
Deerfield, IL 60015 USA
Printed in USA
07-19-42-943
Issued March 2004

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