

FLUCAN

Capsules

Composition

Each capsule contains Fluconazole 50, 100 or 150 mg

Action

Fluconazole is a triazole anti-fungal, which in sensitive fungi, inhibits cytochrome P450-dependent enzymes resulting in impairment of ergosterol synthesis in fungal cell membranes. It 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. It has been demonstrated that fluconazole administration of 50 mg per day for up to 28 days does not influence testosterone plasma concentrations in men or steroid concentrations in fertile women. Fluconazole in a dose of 200-400 mg/day does not have a clinically significant effect on endogenous corticosteroid levels or the ACTH-stimulated response in normal healthy male volunteers.

Fluconazole has been shown to be active in a variety of animal fungal infections. Activity has been demonstrated against opportunistic mycoses e.g. infections with *Candida* spp including systemic candidiasis and in immunocompromised animals, with *Cryptococcus neoformans* including intracranial infections, 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.

The sensitivity of fungal microorganisms to fluconazole is as follows:

Micro-organism	MIC in mcg/ml
<i>Candida albicans</i> (average of 159 isolates)	0.39
Other <i>Candida</i> spp	0.19 to > 25
<i>Cryptococcus neoformans</i> (average of 5 isolates)	1.25
<i>Microsporum</i> spp	9.4 to > 100
<i>Trichophyton</i> spp	37.5 to > 100
<i>Aspergillus</i> spp	> 100

It has been shown that the in-vitro MIC values correlate poorly with the activity of fluconazole in-vivo. This is a general problem seen with the azole antifungals. Most fungi show higher sensitivity to fluconazole in-vivo than in-vitro.

There have been some reports of fluconazole resistance in *Candida albicans* infections in AIDS patients who were being administered fluconazole long-term. Cross-resistance with other azoles has been reported.

Pharmacokinetics

The pharmacokinetic properties of fluconazole are the same following either oral or intravenous administration.

Fluconazole is well absorbed following oral administration with bioavailability from the oral route being 90% or more of that from the intravenous route. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations may occur 0.5-1.5 hours post dose.

The mean plasma elimination half-life is approximately 30 hours but is increased in patients with impaired renal function. Multiple dosing leads to increases in peak plasma concentrations with 90% steady state concentrations being reached in 4-5 days with the once daily dosing regimen although if a loading dose is given on day 1 (twice the usual daily dose) these can be achieved by day 2. Plasma concentrations are dose proportionate.

Fluconazole is widely distributed and the volume of distribution approximates to total body water. Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids, and peritoneal fluids are similar to those achieved in plasma. Concentrations in the cerebrospinal fluid range from 50-90% of plasma concentrations even in the absence of meningeal inflammation. Protein binding is low being only about 12%.

Higher concentrations of fluconazole are reached in the skin, stratus corneum, and epidermis-dermis layer and in endocrine sweat than in the serum. Fluconazole accumulates in the stratus corneum. About 80% or more of a dose is excreted unchanged in the urine and about 11% as metabolites.

There are differences in the pharmacokinetics of fluconazole between adults and children with children after the neonatal period generally having a faster elimination rate and larger volume of distribution than adults do. These differences result in less accumulation on multiple dosing in children with steady state achieved faster than in adults.

Neonates have reduced elimination rates relative to adults and even higher volumes of distribution in comparison to older children. During the first 2 weeks after birth the clearance of fluconazole increases and the half-life decreased as renal function develops. The half-life found in infants was consistent with that found in older children although the Vd was higher. During the first year of life the pharmacokinetics of fluconazole are similar to older children. No marked sex related differences in pharmacokinetics are evident in children. Premature newborns have a lower fluconazole plasma elimination half-life and a large volume of distribution compared with full-term newborns.

Indications

Flucan is indicated for the treatment of the following conditions in adults and children:

- *Cryptococcal meningitis* and maintenance therapy to prevent relapse of Cryptococcal disease in patients with AIDS
- Systemic candidiasis
- Oropharyngeal and esophageal candidiasis
- Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy and radiotherapy

Prophylaxis

Flucan 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.

Contraindications

- Fluconazole is contraindicated in patients who have shown hypersensitivity. There is no information regarding cross hypersensitivity between Fluconazole and otherazole antifungal agents.
- Caution should be used in prescribing Fluconazole to patients with hypersensitivity to other azoles.

Warnings

Hepatic Function

Fluconazole has been associated with 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 patient has been observed. Hepatotoxicity may be reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during Fluconazole therapy should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to Fluconazole.

Patients have less frequently developed pruritis, rashes, urticaria, angioedema, dry skin, abnormal odor, exfoliative cutaneous reactions, such as Steven-Johnson Syndrome and toxic epidermal necrolysis during treatment with Fluconazole. AIDS patients are more prone to the development of severe cutaneous reaction to many drugs. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and Fluconazole discontinued if bullous lesions or erythema multiforme develop.

The co-administration of Fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Dosage in Patients with Impaired Renal Function

Fluconazole is cleared primarily by renal excretion as unchanged drug. No adjustments in single dose therapy are necessary. Multiple-dose therapy should be carefully monitored in patients with renal impairment.

In patients (including children) with impaired renal function, an initial 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:

Dosage and Administration

Creatinine Clearance (ml/min)	Percent of Recommended Dose
>50	100%
≤50	50%
Regular hemodialysis	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:

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

Conversion of serum creatinine units to SI (i.e., micromol/l):

$$\frac{\text{Weight (kg)} \times (140 \text{ minus age})}{88,4 \times 72 \times \text{serum creatinine (mg/dl)}}$$

Females: 0.85 x above value

Adverse Reactions

Central and Peripheral Nervous System

Headache

Dermatologic

Rash. If a rash develops which is considered attributable to Fluconazole, further treatment with this agent should be stopped.

Gastrointestinal

Nausea, vomiting, abdominal pain, diarrhea, and flatulence.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities of hepatic, renal, and hematological function have been observed during treatment with Fluconazole.

Liver/Biliary

Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT

Other side-effects include

Dizziness, seizures, hyperkinesia, hypertonia, vertigo. Alopecia, exfoliative skin disorders including Stevens-Johnson Syndrome and toxic epidermal necrolysis . Dyspepsia .Leucopenia including neutropenia and agranulocytosis, thrombocytopenia. Anaphylaxis (including angioedema, face edema pruritis). Hepatic failure, hepatitis, hepatocellular necrosis, jaundice . Hypercholesterolemia, hypertriglyceridemia, hypokalemia, thirst, polyuria. Insomnia, nervousness. Female sexual dysfunction, intermenstrual bleeding, leucorrhea, and menorrhagia. Fatigue, malaise, rigors, flushing. Taste perversion, abnormal vision

Precautions**Pregnancy***Category C*

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

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

Efficacy of Fluconazole has not been established in children. A small number of patients from age 3 to 13 years have been treated safely with Fluconazole using doses of 3-6 mg/kg daily.

Drug Interactions*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.

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.

Phenytoin

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

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.

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.

Theophylline

Fluconazole increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving Fluconazole and theophylline is recommended.

Terfenadine

Because of the occurrence of serious cardiac dysrhythmias in patients receiving other azole antifungals in conjunction with terfenadine, an interaction study has been performed, and failed to demonstrate a clinically significant drug interaction. Although these events have not been observed in patients receiving Fluconazole, the co-administration of Fluconazole and terfenadine should be carefully monitored. 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.

Dosage and Administration

Dosage and Administration in Adults

Single Dose

Vaginal candidiasis: The recommended dosage of Flucan for vaginal candidiasis is 150 mg as a single oral dose.

Multiple Doses

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 Flucan for the treatment of infections other than vaginal candidiasis should be based in 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 Flucan 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 Flucan 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 50-200 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 10-12 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 Flucan 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 Flucan 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:

<u>Pediatric Patients</u>	<u>Adults</u>
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.

Oropharyngeal candidiasis

The recommended dosage of Flucan 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 Flucan 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 in 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 6-12 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 10-12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of Cryptococcal meningitis in children with AIDS, the recommended dose of Flucan is 6 mg/kg once daily.

Over Dosage

The following events have been reported with an over dosage with Fluconazole: insomnia, irritability, vomiting, diarrhea, abdominal pain/cramps, anorexia, bulging fontanel, elevation of alkaline phosphatase and gamma glutamyl transpeptidase, increase in serum calcium, renal failure, fatigue, facial rash, skin erythema, generalized urticaria, arthralgia, itching, numbness of the tongue and distressed mood.

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%.

Presentation

Flucan 50 mg

Box of 7 capsules

Flucan 100 mg

Box of 7 capsules

Flucan 150 mg

Box of one capsule