



DIFLUCAN[®]
Fluconazole Tablets

S4

Prescription
Required

FOR DIFLUCAN DONATION PROGRAM ONLY

SCHEDULING STATUS

Schedule 4.

PROPRIETARY NAME (AND DOSAGE FORM)

DIFLUCAN TABLETS 200 mg

COMPOSITION

Diflucan (fluconazole) is a bis-triazole: 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol. Fluconazole is a white to off-white crystalline powder which is sparingly soluble in water and saline. It has a molecular weight of 306,3.

Each Diflucan tablet 200 mg contains 200 mg fluconazole

Diflucan tablets contain the following inactive ingredients: Microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone, croscarmellose sodium, FD&C Red No. 40 aluminium lake dye and magnesium stearate.

PHARMACOLOGICAL CLASSIFICATION

A.20.2.2 Fungicides.

PHARMACOLOGICAL ACTION

Fluconazole, a member of the triazole antifungal agents, is an inhibitor of fungal sterol synthesis.

After oral administration in adults, fluconazole is well absorbed with systemic bioavailability being over 90%. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post dose with a plasma elimination half-life of approximately 30 hours. Plasma protein binding is low (12%).

Pharmacokinetic studies performed in children have shown that fluconazole is cleared faster than in adults, with a half-life of 23 hours. The volume of distribution of fluconazole in children under 1 year of age (950 ml/kg) is higher than in adults (700 ml/kg). Accumulation on multiple daily dosing is therefore less and steady-state plasma levels are achieved faster than in adults.

In neonates, the half lives determined over the first 2 weeks of life are considerably longer than adult values with a mean of 74 hours at Day 1 and 47 hours at Day 13 of life. The volume of distribution is about 1200 ml/kg in neonates.

The major route of excretion is renal with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites, but accumulation is significant over 15 days and concentrations may rise 2-3 fold.

The long plasma elimination half-life (approximately 30 hours) provides the basis for once daily dosing in the treatment of systemic conditions and single dose therapy for vaginal candidiasis.

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.

Fluconazole is highly specific for fungal cytochrome P-450 dependant enzymes. Fluconazole has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age.

INDICATIONS

Once the results of cultures and other laboratory studies become available, anti-infective therapy should be adjusted accordingly.

Fluconazole is indicated for the treatment of the following conditions:

1. Cryptococcal meningitis and maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS
2. Systemic candidiasis
3. Oropharyngeal and oesophageal candidiasis
4. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy and radiotherapy

CONTRAINDICATIONS

Fluconazole should not be used in patients with known sensitivity to the medicine or to related azole compounds.

Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. (See Interactions section)

Co-administration of cisapride is contraindicated in patients receiving fluconazole.

Pregnancy.

Lactation, as fluconazole is found in breast milk at concentrations similar to plasma.

WARNINGS

Use during pregnancy and lactation

There are no adequate and well controlled studies which assessed the safety of fluconazole treatment in pregnant women. There have been reports of congenital abnormalities in infants whose mothers were treated with fluconazole. The relationship between fluconazole use and these events is unclear.

Effects on ability to drive and use machines

Experience with fluconazole indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

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 pruritus, rashes, urticaria, angioedema, dry skin, abnormal odour, exfoliative cutaneous reactions, such as Stevens-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. (See Interactions section)

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 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 DIFLUCAN

Creatinine Clearance (ml/min)

> 50

? 50

Regular haemodialysis

Percent of Recommended Dose

100%

50%

One recommended dose 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:

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

Females : 0.85 x above value

DOSAGE AND DIRECTIONS FOR USE

The daily dose of fluconazole should be based on the nature and severity of the fungal infection.

Therapy for those types of infections requiring multiple dose 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.

Use in Adults

1. For cryptococcal meningitis the usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response of the patient this dose may be increased to 400 mg daily. Usually, duration of treatment for cryptococcal meningitis is 6-8 weeks.

For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient received a full course of primary therapy, fluconazole may be administered at a daily dose of 100 to 200 mg.

2. For systemic candidiasis the usual dose is 400 mg on the first day followed by 200 mg daily. Depending on the clinical response, the dose may be increased to 400 mg daily. Duration of treatment is based upon the clinical response.
3. For oropharyngeal candidiasis, the usual dose is 50 to 100 mg once daily for 7-14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function.

For the prevention of relapse of oropharyngeal candidiasis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a 150 mg once weekly dose.

For oesophageal candidiasis, the recommended dose is 200 mg on the first day, followed by 100 mg to 200 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 oesophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.

4. The recommended fluconazole dosage for the prevention of candidiasis is 50 mg to 400 mg once daily, based on the patients risk for developing fungal infection. For patients at high risk of systemic infection e.g. patients who are anticipated to have profound or prolonged neutropenia, a dose of 400 mg once daily has been used. Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells per mm³.

Use in Elderly

Where there is no evidence of renal impairment, normal dosage recommendations should be adopted.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

The commonest side-effects associated with fluconazole are:

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, diarrhoea and flatulence.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities of hepatic, renal and haematological function have been observed during treatment with fluconazole (see "Warnings").

Liver/Biliary: Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

Other side-effects include:

Central and Peripheral Nervous System: Dizziness, seizures, hyperkinesia, hypertonia, vertigo.

Dermatologic: Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis (See "Warnings").

Gastrointestinal: Dyspepsia.

Haematopoetic and Lymphatic: Leucopenia including neutropenia and agranulocytosis, thrombocytopenia.

Immunologic: Anaphylaxis (including angioedema, face edema, pruritus)

Liver/Biliary: Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional: Hypercholesterolemia, hypertriglyceridemia, hypokalemia, thirst, polyuria.

Psychiatric: Insomnia, nervousness.

Reproductive: Female sexual dysfunction, intermenstrual bleeding, leukorrhoea and menorrhagia.

Body as a whole: Fatigue, malaise, rigors, flushing.

Other senses: Taste perversion, abnormal vision.

Interactions

Fluconazole has been shown to prolong prothrombin times in subjects receiving warfarin. In post-marketing experience, 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. In concomitant treatment with fluconazole and coumarin medicines the dose of anticoagulant should be carefully titrated and the prothrombin time should be carefully monitored. Particular attention should be paid to such patients requiring minor oral surgery and dental procedures.

Benzodiazepines (Short Acting): Following oral 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 is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas.

No clinically significant interactions have been seen with co-administration of oral contraceptives, or cimetidine. No adverse effect has been seen on endogenous steroid levels or on ACTH stimulated cortisol response.

A kinetic study in renal transplant patients found fluconazole 200 mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100 mg daily, fluconazole did not affect cyclosporin levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.

Co-administration of multiple doses of hydrochlorothiazide may increase the plasma concentrations of fluconazole.

Concomitant administration of Diflucan and phenytoin may increase the levels of phenytoin to a clinical significant degree.

Concomitant administration of fluconazole and theophylline may increase the risk of theophylline toxicity due to a fluconazole induced decrease in plasma theophylline clearance.

Concomitant administration of Diflucan and rifampicin has resulted in a 25% decrease in the AUC and 20% shorter half-life of fluconazole.

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200 mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment, cross-over study examined zidovudine levels in HIV patients. On two occasions, 21 days apart, patients received zidovudine 200 mg every eight hours either with or without fluconazole 400 mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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 is contraindicated (See contraindications). The co-administration of fluconazole at doses lower than 400 mg per 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. Co-administration of cisapride is contraindicated in patients receiving fluconazole.

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

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

The use of fluconazole in patients concurrently taking astemizole or other medicines metabolised by the cytochrome P-450 system may be associated with elevations in serum levels of these medicines. In the absence of definitive information, caution should be used when coadministering fluconazole. Patients should be carefully monitored. (See warnings)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

In the advent of overdosage, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

Fluconazole is largely excreted in the urine; forced diuresis would probably increase the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

IDENTIFICATION

Pink trapezoidal tablets engraved with 'DIFLUCAN' and '200' on the front and 'ROERIG' on the back.

PRESENTATION

Blue-white HDPE bottles containing 28 tablets.

STORAGE INSTRUCTIONS

Store below 30°C. Keep out of reach of children.

REGISTRATION NUMBER

35/20.2.2/0187

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DATE OF PUBLICATION OF THIS PACKAGE INSERT

24 November 2000