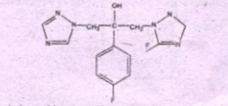
Pfizer

ڈائی فلوکین

Diflucan®
(Fluconazole)

DESCRIPTION

Diflucan® (fluconazole), the first of a new subclass of synthetic triazole antifungal agents, is available as capsules for oral administration and as a sterile solution for intravenous use. Fluconazole is designated chemically as 2,4-difluoro-bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol with an empirical formula of $C_{13}H_{12}F_2N_6O$ and molecular weight 306.3. The structural formula is:



Fluconazole is a white crystalline solid which is slightly soluble in water and saline. Diflucan® capsules contain 50, 150 and 200 mg of fluconazole. Diflucan® injection is an iso-osmotic, sterile, non pyrogenic solution of fluconazole in a sodium chloride or dextrose diluent.

THERAPEUTIC INDICATIONS

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.

- **Cryptococcosis**, including cryptococcal meningitis and infections of other sites (e.g., pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.
- **Systemic candidiasis**, including candidemia, disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium, eye, and pulmonary and urinary tracts. Patients with malignancy, in intensive care units, receiving cytotoxic or immunosuppressive therapy, or with other factors predisposing to candidal infection may be treated.
- **Mucosal candidiasis.** These include oropharyngeal, esophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated. Prevention of relapse of oropharyngeal candidiasis in patients with AIDS.
- **Genital candidiasis.** Vaginal candidiasis, acute or recurrent; and prophylaxis to reduce the incidence of recurrent vaginal candidiasis in 4 or more episodes a year). Candidal balanitis.
- **Prevention of fungal infections** in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy or radiotherapy.
- **Dermatomycosis** including tinea pedis, tinea corporis, tinea cruris, tinea versicolor, tinea unguium (onychomycosis), and dermal candida infections.
- **Deep endemic mycoses** in immuno-competent patients, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis and histoplasmosis.

POSOLOGY AND METHOD OF ADMINISTRATION

The daily dose of Diflucan® (fluconazole) should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. 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 and cryptococcal infections at other sites, the usual dose is 400 mg on the first day followed by 200 to 400 mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6-8 weeks for cryptococcal meningitis.

For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, Diflucan® may be administered indefinitely at a daily dose of 200 mg.

2. For candidemia, disseminated candidiasis and other invasive candidal infections, 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 atrophic oral candidiasis associated with dentures, the usual dose is 50 mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.

For other candidal infections of mucosa except genital candidiasis (e.g., esophagitis, non-invasive broncho-pulmonary infections, candiduria, mucocutaneous candidiasis, etc.) the usual effective dose is 50 to 100 mg daily, given for 14-30 days.

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

4. For the treatment of vaginal candidiasis, Diflucan® 150 mg should be administered as a single oral dose.

To reduce the incidence of recurrent vaginal candidiasis, a 150 mg once monthly dose may be used. The duration of therapy should be individualized, but ranges from 4-12 months. Some patients may require more frequent dosing.

For Candida balanitis, Diflucan® 150 mg should be administered as a single oral dose.

5. The recommended Diflucan® dosage for the prevention of candidiasis is 50 to 400 mg once daily, based on the patient's 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, the recommended daily dose is 400 mg once daily. Diflucan® 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.

6. For dermal infections including tinea pedis, corporis, cruris and candida infections, the recommended dosage is 150 mg once weekly or 50 mg once daily. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks.

For tinea versicolor, the recommended dose is 300 mg once weekly for 2 weeks; a third weekly dose of 300 mg may be needed in some patients, whereas, in some patients, a single dose of 300 to 400 mg may be sufficient. An alternate dosing regimen is 50 mg once daily for 2 to 4 weeks.

For tinea unguium, the recommended dosage is 150 mg once weekly. Treatment should be continued until infected nail is replaced (uninfected nail grows in). Re-growth of fingernails and toenails normally requires 3 to 6 months and 6 to 12 months, respectively. However, growth rates may vary widely in individuals, and by age. After successful treatment of long-term chronic infections, nails occasionally remain disfigured.

7. For deep endemic mycoses, doses of 200 to 400 mg daily for up to 2 years may be required. The duration of therapy should be individualized but ranges from 11-29 months with coccidioidomycosis, 2-17 months with paracoccidioidomycosis, 1-16 months with sporotrichosis and 3-17 months for histoplasmosis.

Use in Children: As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. The maximum adult daily dosage should not be exceeded in children. Diflucan® is administered as a single dose each day.

The recommended dosage of Diflucan® for mucosal candidiasis is 3 mg/kg daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady state levels more rapidly.

For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6 to 12 mg/kg daily, depending on the severity of the disease.

For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of Diflucan® is 6 mg/kg once daily.

For the prevention of fungal infections in immuno-compromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 to 12 mg/kg daily, depending on the extent and duration of the induced neutropenia (see Use in Adults). (For children with impaired renal function, see Use in Renal Impairment).

Use in Children 4 weeks of age and younger: Neonates excrete Diflucan® (fluconazole) slowly. In the first two weeks of life, the same mg/kg dosing as in older children should be used but administered every 72 hours. During weeks 3 and 4 of life, the same dose should be given every 48 hours.

Use in Elderly: Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance <50 ml/min) the dosage schedule should be adjusted as described below.

Use in Renal Impairment: Diflucan® (fluconazole) is predominantly excreted in the urine as unchanged drug. No adjustments in single-dose therapy are necessary. In patients (including children) with impaired renal function who will receive multiple doses of Diflucan®, 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

Patients on regular dialysis should receive 100% of the recommended dose after each dialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance

Administration

Diflucan® may be administered either orally or by intravenous infusion at a rate not exceeding 10 ml/minute, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or vice versa, there is no need to change the daily dosage. Diflucan® I.V. is formulated in 0.9% sodium chloride solution, each 200 mg (100 ml bottle) containing 15 mmol each of Na^+ and Cl^-. Because Diflucan® is available as a dilute saline solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

CONTRAINDICATIONS

Diflucan® (fluconazole) should not be used in patients with known sensitivity to the drug, any of the inert ingredients or to related azole compounds.

Co-administration of terfenadine is contraindicated in patients receiving Diflucan® (fluconazole) at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Co-administration of other drugs known to prolong the QT interval and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, pimozide and quinidine are contraindicated in patients receiving Diflucan® (fluconazole) (see sections **Special Warnings and Special Precautions for Use and Interaction with Other Medicaments and Other Forms of Interaction**).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluconazole should be administered with caution to patients with liver dysfunction

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 patient has been observed. Fluconazole hepatotoxicity has usually been 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 rarely developed 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 reactions to many drugs. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this agent should be discontinued.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/day with terfenadine should be carefully monitored (see sections **Contraindications and Interaction with Other Medicaments and Other Forms of Interaction**).

In rare cases, as with other azoles, anaphylaxis has been reported.

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.

Fluconazole should be administered with caution to patients with renal dysfunction (see also **Posology and Method of Administration**).

Fluconazole) is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolised through CYP2C9 and CYP3A4 should be monitored (see section **Interaction with Other Medicaments and Other Forms of Interaction**).

Fluconazole capsules contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Concomitant use of the following other medicinal products are contraindicated:

- Cisapride: There have been reports of cardiac events including Torsade de Pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated in patients receiving fluconazole (see section **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. 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 section **Contraindications**). The co-administration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.
- Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and astemizole is contraindicated (see section **Contraindications**).
- Pimozide: Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and pimozide is contraindicated (see section **Contraindications**).

Concomitant use of the following other medicinal products cannot be recommended:

- Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. This combination should be avoided.

Concomitant use of the following other medicinal products lead to precautions and dose adjustments:
The effect of other medicinal products on Diflucan® (fluconazole)

- Hydrochlorothiazide: In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.
- Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and a 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.

The effect of Diflucan® (fluconazole) on other medicinal products

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 co-administered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists for 4 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.

- Alfentanil: A study observed a reduction in clearance and distribution volume as well as prolongation of $T\frac{1}{2}$ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.
- Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5- nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and

after one week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

- Amphotericin B: 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 Cryptococcus neoformans, and antagonism of the two drugs in systemic infection with A. fumigatus. The clinical significance of results obtained in these studies is unknown.

- Anticoagulants: In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experience, as with other 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 in patients receiving coumarin-type anticoagulants should be carefully monitored. Dose adjustment of warfarin may be necessary.

- Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

- 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 increases the AUC of triazolam (single dose) by approximately 50%, Cmax with 20-32% and increases t½ by 25-50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

- Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed.There is a risk of developing carbemazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

- Calcium Channel Blockers: Certain dihydropyridine calcium channel antagonists (nifedipine, isradipine, amlodipine and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

- Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg) the celecoxib Cmax and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

- Cyclosporin: Fluconazole significantly increases the concentration and AUC of cyclosporin. This combination may be used by reducing the dosage of cyclosporin depending on cyclosporin concentration.

- Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

- Fentanyl: One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomized crossover study with twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

- Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4.

- HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

- Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite E-31 741 which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

- Methadone: Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

- Non-steroidal anti-inflammatory drugs: The Cmax and AUC of flurbiprofen were increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] were increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

  Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

- Oral Contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive. ,

- Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

- Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

- Rifabutin: There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80%. 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.

- Saquinavir: Fluconazole increases the AUC of saquinavir with approximately 50%, Cmax with approximately 55% and decreases clearance of saquinavir with approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

- Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

- Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during coadministration.

- Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

- Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and therapy modified appropriately if signs of toxicity develop.

- Vinca Alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

- Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoic acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind

- Zidovudine: Fluconazole increases Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but such interactions may occur.

Pregnancy and Lactation

Use during Pregnancy: Data from several hundred pregnant women treated with doses <200 mg/day of Diflucan® (fluconazole), administered as a single or repeated dosage in the first trimester, show no undesired effects in the fetus

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) Diflucan® (fluconazole) therapy for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high dose levels associated with maternal toxicity. There was no fetal oncogenicity at 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 20-60x 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.

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom Diflucan® (fluconazole) may be used if the anticipated benefit outweighs the possible risk to the fetus.

Use during Lactation: Diflucan® (fluconazole) is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

UNDESIRABLE EFFECTS

Diflucan® (fluconazole) is generally well tolerated.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities (see section **Special Warnings and Special Precautions for Use**) have been observed during treatment with Diflucan® and comparative agents, but the clinical significance and relationship to treatment is uncertain.

The following undesirable effects have been observed and reported during treatment with Diflucan® with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data).

Pediatric Population: The pattern and incidence of adverse events and laboratory abnormalities recorded during pediatric clinical trials are comparable to those seen in adults.

System Organ Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylaxis, angioedema
Metabolism and nutrition disorders	Rare	Hypertriglyceredemia, hypercholesterolemia, Hypokalaemia
Psychiatric disorders	Uncommon	Insomnia, somnolence
Nervous system disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, taste perversion
	Rare	Tremor
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Rare	Torsade de pointes, QT prolongation
Gastrointestinal disorders	Common	Abdominal pain, diarrhea, nausea, vomiting
	Uncommon	Dyspepsia, flatulence, dry mouth
Hepato-biliary disorders	Common	Alanine aminotransferase increased, aspartate amino transferase increased, blood alkaline phosphatase increased
	Uncommon	Cholestasis, jaundice, bilirubin increased
	Rare	Hepatic toxicity, including rare cases of fatalities, Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Pruritus, urticaria, increased sweating, drug eruption
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, dermatitis exfoliative, face edema, alopecia
Musculoskeletal, connective tissue and bone disorders	Uncommon	Myalgia
General disorders and administration site conditions	Uncommon	Fatigue, malaise, asthenia, fever

OVERDOSAGE

There have been reports of overdose with Diflucan® (fluconazole) accompanied by hallucination and paranoid behaviour. In the event of over dosage, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Diflucan® is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

SHELF LIFE

Diflucan® (fluconazole) should not be used beyond the expiry date.

- Capsules: 36 months
- Intravenous infusion: 24 months

HOW SUPPLIED

Diflucan® (fluconazole) is available with the following presentations

- 50 mg capsules: 7's blister pack
- 150 mg capsules: 1's blister pack
- 200 mg capsules: 4's blister pack
- Intravenous infusion: 50mL vial

Diflucan® (fluconazole) intravenous infusion is compatible with the following administration fluids:

a) Dextrose 20%
b) Ringer's solution
c) Hartmann's solution
d) Potassium chloride in dextrose
e) Sodium bicarbonate 4.2%
f) Aminofusin
g) Normal saline

Diflucan® (fluconazole) may be infused through an existing line with one of the above listed fluids. Although no specific incompatibilities have been noted, mixing with any other drug prior to infusion is not recommended.

DOSAGE

Use as directed by the physician.

INSTRUCTIONS

Avoid exposure to heat & sunlight.
Store in a dry place below 30°C.
Keep out of the reach of children.

CAUTION

To be sold on the prescription of a registered medical practitioner only.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دوا کو گرمی اور سورج کی روشنی سے بچائیں۔

۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ میں رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

تاکید: صرف رجسٹرڈ میڈیکل پریکٹشنر کے نسخہ پر فروخت کریں۔

Pfizer

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