

Fluconazole

Brand Name: Diflucan



Drug Description

Fluconazole, a synthetic triazole derivative, is an azole antifungal agent. [1]

HIV/AIDS-Related Uses

Oral or intravenous (IV) fluconazole is used in the treatment of oropharyngeal, esophageal, and vulvovaginal candidiasis in immunocompromised adults with AIDS, advanced AIDS-related complex, malignancy, or other serious underlying disease. Fluconazole appears to be at least as effective, and in some cases more effective, than other antifungal agents used in the initial treatment of these candidal infections and is considered a drug of choice. HIV-infected patients with severe or recurrent episodes of these types of candidiasis may benefit from long-term suppressive or maintenance therapy with fluconazole to prevent relapse.[2] Fluconazole may also be used for primary prophylaxis and for long-term suppressive or chronic maintenance therapy to prevent recurrence or relapse of serious fungal infections in patients considered at high risk for developing such infections, such as those with AIDS. These infections include blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, and mucocutaneous candidiasis.[3]

Fluconazole is also indicated for the treatment and suppression of cryptococcal meningitis as a less toxic (albeit less efficacious) course of treatment than amphotericin B plus flucytosine in AIDS patients. Although amphotericin B (with or without flucytosine) has been considered the initial treatment of choice for cryptococcal meningitis, fluconazole is an alternative for these infections in patients whose disease is not severe, since it is well tolerated and is distributed into cerebrospinal fluid (CSF) at high concentrations. In maintenance therapy, fluconazole is usually better tolerated than amphotericin B alone.[4] [5]

Non-HIV/AIDS-Related Uses

Fluconazole is indicated in the prophylaxis and treatment of esophageal, oropharyngeal, disseminated, chronic mucocutaneous, and

vulvovaginal candidiasis; coccidioidomycosis; cryptococcal meningitis; onychomycosis; febrile neutropenia; fungal pneumonia; fungal septicemia; tinea corporis, tinea cruris, tinea pedis, and tinea manuum.[6]

Fluconazole is FDA approved for the treatment of systemic candidal infections and is an appropriate, less toxic alternative to amphotericin B.[7]

Pharmacology

Fluconazole is fungistatic and may be fungicidal, depending on the concentration. Azole antifungals interfere with fungal cytochrome P450 enzyme activity necessary for the demethylation of 14-alpha-methyl sterols to ergosterol, the principal sterol in fungal cell membranes. As ergosterol is depleted, the fungal cell membrane is damaged. Unlike ketoconazole, fluconazole has a very weak, noncompetitive inhibitory effect on the liver cytochrome P450 enzyme system, while maintaining a high affinity for fungal cytochrome P450 enzyme activity. In *Candida albicans*, azole antifungals inhibit transformation of blastospores into invasive mycelial form. Fluconazole has not been reported to have antiandrogenic activity at currently used doses, and does not affect cortisol metabolism in patients treated with clinically recommended doses.[8]

Fluconazole is rapidly and almost completely absorbed from the gastrointestinal (GI) tract. Oral bioavailability of fluconazole exceeds 90% in healthy, fasting adults; peak plasma concentrations of the drug are generally attained within 1 to 2 hours after oral administration; limited studies indicated that bioavailability for adults with HIV appears to be similar to that seen in healthy adults. Unlike other antifungal agents (e.g., itraconazole and ketoconazole), GI absorption of fluconazole does not appear to be affected by gastric pH.[9]

Following oral or IV administration, fluconazole is widely distributed throughout the body, with good penetration of CSF (ranging from 52% to 85% of concurrent plasma concentrations in patients with fungal meningitis), the eye, and peritoneal fluid.[10] The apparent volume of distribution of

Fluconazole

Pharmacology (cont.)

fluconazole approximates that of total body water and has been reported to be 0.7 L/kg to 1 L/kg. It is not known if fluconazole crosses the placenta, but fluconazole is distributed into human milk in concentrations similar to those attained in plasma.[11]

Fluconazole is in FDA Pregnancy C. Adequate and well-controlled studies have not been done in pregnant women. Fertility was not affected in male or female rats treated with oral daily doses of 5 mg/kg to 20 mg/kg or parenteral doses of 5, 25, or 75 mg/kg, although the onset of parturition was slightly delayed with oral doses of 20 mg/kg. Maternal weight gain impairment and abortions occurred in pregnant rabbits given 75 mg/kg oral doses (20 to 60 times the recommended human dose). No adverse fetal effects were detected. Oral doses of 25 mg/kg fluconazole given to pregnant rats caused impaired maternal weight gain and increased placental weight, with a slight increase in the number of stillborn pups and a decrease in neonatal survival. At higher doses, supernumerary ribs, renal pelvis dilation, and ossification delays were observed. In rats, deaths of embryos and fetal abnormalities, including wavy ribs, cleft palate, and abnormal craniofacial ossification, occurred at fluconazole doses ranging from 80 mg/kg to 320 mg/kg (approximately 20 to 60 times the recommended human dose). 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. This effect has not been observed in women treated with fluconazole.[12]

Unlike itraconazole and ketoconazole, fluconazole exhibits very low binding to proteins (11%). Metabolism of fluconazole is primarily hepatic. Biliary excretion of fluconazole occurs but only in a very small amount.[13] The plasma elimination half-life of fluconazole in healthy adults is approximately 30 hours (ranging from 20 hours to 50 hours). In patients with impaired renal function, plasma concentrations of fluconazole are higher and the half-life prolonged; elimination half-life of the drug is inversely proportional to the patient's creatinine clearance.[14]

Fluconazole is largely excreted in urine, and fluconazole elimination is principally renal. Renal clearance of the drug averages 0.27 ml/min per kg in adults with normal renal function.

Approximately 60% to 80% of a single oral or IV dose of fluconazole is excreted in urine unchanged, and about 11% is excreted in urine as metabolites. Small amounts of the drug are excreted in feces. Fluconazole is removed by hemodialysis and peritoneal dialysis. A three-hour hemodialysis session decreases plasma levels by approximately 50%.[15] [16]

Resistance to fluconazole can be produced in vitro by serial passage of *Candida albicans* in the presence of increasing concentrations of the drug. Some *Candida* species are intrinsically resistant to fluconazole (e.g., *C. krusei*) and many strains of *C. glabrata* are resistant to the drug. Prolonged or intermittent use of oral fluconazole in immunocompromised patients has been suggested as a major contributing factor to the emergence of fluconazole resistance in *Candida*. Fluconazole-resistant fungi may also be cross-resistant to other azole antifungal agents (e.g., itraconazole and ketoconazole). While the clinical importance is unclear, fluconazole-resistant strains of *C. albicans* that were cross-resistant to amphotericin B have been isolated from a few immunocompromised individuals, including patients with leukemia and HIV.[17]

Adverse Events/Toxicity

Adverse effects seen with azole antifungals include hypersensitivity; agranulocytosis; exfoliative skin disorders, including Stevens-Johnson syndrome; hepatotoxicity; thrombocytopenia; central nervous system effects; and gastrointestinal disturbances.[18]

The most common adverse events to fluconazole in pharmacological testing have been headache, nausea, and abdominal pain. Clinical adverse effects were reported more frequently in HIV infected patients than in HIV uninfected patients.[19] There is an increased risk of exfoliative skin disorders, such as Stevens-Johnson syndrome, agranulocytosis, and thrombocytopenia, with the use of fluconazole.[20]

Fluconazole

Drug and Food Interactions

The rate and extent of GI absorption of fluconazole is not affected by food.[21]

In addition to those drugs contraindicated with its use, there are many drugs that may produce interactions if taken concurrently with fluconazole. Concurrent use of fluconazole with oral antidiabetic agents, such as tolbutamide, chlorpropamide, glyburide, or glipizide, has increased the plasma concentrations of these sulfonylurea agents; hypoglycemia has been noted and blood glucose concentrations should be monitored, as the dose of oral hypoglycemia agent may need to be reduced. The anticoagulant effects of warfarin may be increased when warfarin is used concurrently with any azole antifungal, resulting in an increase of prothrombin time; patients on such a regimen should be monitored carefully. Anticonvulsants (e.g., carbamazepine, phenobarbital, and phenytoin) may decrease fluconazole plasma concentrations, leading to treatment failure or clinical relapse. Use of immunosuppressive drugs such as cyclosporine, methylprednisolone, sirolimus, and tacrolimus or the antiasthmatic theophylline with concurrent fluconazole should be monitored carefully because fluconazole may inhibit their metabolism, increasing the plasma concentration of these drugs to toxic levels. Use of fluconazole with astemizole and other drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. Rifampin and rifabutin may increase the metabolism of fluconazole and other azoles, lowering the plasma concentration, which may lead to clinical failure or relapse.[22] [23]

Amphotericin B may have an antagonistic relationship with fluconazole, but it is unclear if such antagonism actually occurs in vivo. Flucytosine may have a synergistic, additive, or indifferent effect when used with fluconazole, possibly because fluconazole damages the fungal cell membrane, allowing greater intercellular penetration of flucytosine. Central nervous system toxicity has been reported when amitriptyline, a tricyclic antidepressant, is used concurrently with fluconazole; increased serum concentrations of amitriptyline have been observed and are presumed to be related to fluconazole interfering with

amitriptyline metabolism. Concurrent use of thiazide diuretics with fluconazole may increase peak fluconazole plasma concentrations, presumably due to the diuretic decreasing renal clearance of fluconazole by as much as 20%.[24]

Concomitant administration of fluconazole with HIV protease inhibitors (PIs) may have clinically important effects; use with indinavir may result in a decrease in serum concentrations of indinavir, while use with zidovudine may result in an increase in serum concentrations of zidovudine. Fluconazole may interfere with zidovudine metabolism and increase serum concentrations of this nucleoside reverse transcriptase inhibitor.[25]

Contraindications

Fluconazole is contraindicated for patients who have shown hypersensitivity to fluconazole and should be prescribed with caution to patients with hypersensitivity to other azoles. Coadministration of fluconazole with cisapride or terfenadine is contraindicated because of reports of cardiac event, including torsade de pointes and serious cardiac dysrhythmias.[26]

Clinical Trials

For information on clinical trials that involve Fluconazole, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Fluconazole AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (tablet and suspension) and intravenous (in dextrose or sodium chloride diluent).[27]

Dosage Form: Fluconazole tablets containing 50 mg, 100 mg, 150 mg, and 200 mg.[28]

Fluconazole oral suspension; 350 mg in 35-ml bottles (10 mg/ml); 1400 mg in 35-ml bottles (40 mg/ml).[29]

Fluconazole injection in 5.6% dextrose diluent in Viaflex Plus plastic containers, 200 mg/100 ml (2 mg/ml); 400 mg/200 ml (2 mg/ml).[30]

Fluconazole

Dosing Information (cont.)

Fluconazole injection in 0.9% sodium chloride in glass bottles or Viaflex Plus plastic containers, 200 mg/100 ml (2 mg/ml); 400 mg/200 ml (2 mg/ml). [31]

Storage: Fluconazole tablets and oral suspension should be stored below 40 C (104 F), preferably between 5 C and 30 C (41 F to 86 F), in a well-closed container. Reconstituted oral suspension should be protected from freezing and stored between 5 C and 30 C (41 F to 86 F), with unused portions discarded after 2 weeks.

Fluconazole injection in glass bottles should be protected from freezing and stored between 5 C and 30 C (41 F to 86 F). Fluconazole injection in Viaflex Plus plastic containers should be protected from freezing and stored between 5 C and 25 C (41 F to 77 F). Brief exposures to temperatures up to 40 C (104 F) will not adversely affect the product.[32] [33]

Chemistry

CAS Name: 1H-1,2,4-Triazole-1-ethanol, alpha-

Fluconazole



Chemistry (cont.)

CAS Number: 86386-73-4[35]

Molecular formula: C₁₃H₁₂F₂N₆O[36]

C50.98%, H3.95%, F12.41%, N27.44%,
O5.22%[37]

Molecular weight: 306.27[38]

Melting point: 138 to 140 C[39]

Physical Description: Fluconazole is a white crystalline solid that is slightly soluble in water and saline.[40]

Stability: Fluconazole injection has been used safely for up to 14 days of intravenous therapy. The oral suspension should be shaken well before using and stored between 5 C and 30 C (41 F to 86 F); unused portions should be discarded after 2 weeks.[41]

Solubility: Fluconazole is slightly soluble in water (aqueous solubility of 8 mg/ml at 37 C); solubility in alcohol is 25 mg/ml at room temperature.[42]

Other Names

UK-49858[43]

Fluconazol[44]

Further Reading

Bruno R, Sacchi P, Filice G. Overview on the incidence and the characteristics of HIV-related opportunistic infections and neoplasms of the heart: impact of highly active antiretroviral therapy. *AIDS*. 2003 Apr;17 Suppl 1:S83-7. Review. PMID: 12870535

Odds FC, Brown AJ, Gow NA. Antifungal agents: mechanisms of action. *Trends Microbiol*. 2003 Jun;11(6):272-9. Review. PMID: 12823944

Yamada H, Kotaki H, Takahashi T. Recommendations for the treatment of fungal pneumonias. *Expert Opin Pharmacother*. 2003 Aug;4(8):1241-58. PMID: 12877634

Fluconazole



Manufacturer Information

Fluconazole
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

Diflucan
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. AHFS Drug Information - 2003; p. 90
2. AHFS Drug Information - 2003; p. 90-91
3. AHFS Drug Information - 2003; p. 92-94
4. USP DI - 2003; p. 305
5. AHFS Drug Information - 2003; p. 92
6. USP DI - 2003; p. 304-305
7. USP DI - 2003; p. 304-305
8. USP DI - 2003; p. 305-306
9. AHFS Drug Information - 2003; p. 100
10. USP DI - 2003; p. 306
11. AHFS Drug Information - 2003; p. 101
12. USP DI - 2003; p. 313

Fluconazole



13. USP DI - 2003; p. 313
14. AHFS Drug Information - 2003; p. 101
15. AHFS Drug Information - 2003; p. 101
16. Pfizer - Diflucan - Prescribing Information, p. 13. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
17. USP DI - 2003; p. 306
18. USP DI - 2003; p. 309
19. Pfizer - Diflucan - Prescribing Information, p. 11. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
20. USP DI - 2003; p. 309
21. AHFS Drug Information - 2003; p. 100
22. Pfizer - Diflucan - Prescribing Information, p. 8-10. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
23. USP DI - 2003; p. 307-308
24. AHFS Drug Information - 2003; p. 97-99
25. AHFS Drug Information - 2003; p. 97-99
26. Pfizer - Diflucan - Prescribing Information, p. 8-9. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
27. AHFS Drug Information - 2003; p. 101
28. AHFS Drug Information - 2003; p. 101
29. Pfizer - Diflucan - Prescribing Information, p. 16-17. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
30. Pfizer - Diflucan - Prescribing Information, p. 16-17. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
31. Pfizer - Diflucan - Prescribing Information, p. 16-17. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
32. USP DI - 2003; p. 310-311
33. Pfizer - Diflucan - Prescribing Information, p. 16-17. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
34. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/04/03.
35. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/04/03.
36. Merck Index - 2001; p. 728
37. Merck Index - 2001; p. 728
38. Merck Index - 2001; p. 728
39. Merck Index - 2001; p. 728
40. Pfizer - Diflucan - Prescribing Information, p. 1. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
41. Pfizer - Diflucan - Prescribing Information, p. 15. Available at <http://www.diflucan.com/pi.asp>. Accessed 12/04/03.
42. AHFS Drug Information - 2003; p. 101
43. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/04/03.
44. ChemIDplus. - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/>. Accessed 12/04/03.