Fluconazole *(BAN, USAN, rINN)*

Fluconazol; Fluconazolum; Flukonatsoli; Flukonazol; UK-49858. 2-(2,4-Difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

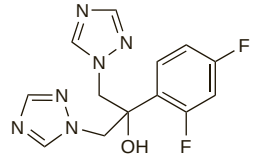
Флуконазол

$C_{13}H_{12}F_2N_6O$ = 306.3.

CAS — 86386-73-4.

ATC — D01AC15; J02AC01.

ATC Vet — QD01AC15; QJ02AC01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*

Ph. Eur. 6.2 (Fluconazole). A white or almost white, hygroscopic, crystalline powder. It exhibits polymorphism. Slightly soluble in water; freely soluble in methyl alcohol; soluble in acetone. Store in airtight containers.

USP 31 (Fluconazole). A white or almost white, crystalline powder. Slightly soluble in water; soluble in alcohol and in acetone; sparingly soluble in chloroform and in isopropyl alcohol; freely soluble in methyl alcohol; very slightly soluble in toluene. Store in airtight containers at a temperature below 30°.

Incompatibility and stability. References.

1. Lor E, *et al.* Visual compatibility of fluconazole with commonly used injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1991; **48:** 744–6.
2. Couch P, *et al.* Stability of fluconazole and amino acids in parenteral nutrient solutions. *Am J Hosp Pharm* 1992; **49:** 1459–62.
3. Hunt-Fugate AK, *et al.* Stability of fluconazole in injectable solutions. *Am J Hosp Pharm* 1993; **50:** 1186–7.
4. Ishisaka DY. Visual compatibility of fluconazole with drugs given by continuous infusion. *Am J Hosp Pharm* 1994; **51:** 2290 and 2292.

Adverse Effects

Adverse effects reported with fluconazole most commonly affect the gastrointestinal tract and include abdominal pain, diarrhoea, flatulence, nausea and vomiting, and taste disturbance. Other adverse effects include headache, dizziness, leucopenia, thrombocytopenia, hyperlipidaemias, and raised liver enzyme values. Serious hepatotoxicity has been reported in patients with severe underlying disease such as AIDS or malignancy. Anaphylaxis and angioedema have been reported rarely.

Skin reactions are rare but exfoliative cutaneous reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred, more commonly in patients with AIDS.

Alopecia. Alopecia has occasionally been reported in patients receiving fluconazole, especially during prolonged use.[1,2]

1. Weinroth SE, Tuazon CU. Alopecia associated with fluconazole treatment. *Ann Intern Med* 1993; **119:** 637.
2. Pappas PG, *et al.* Alopecia associated with fluconazole therapy. *Ann Intern Med* 1995; **123:** 354–7.

Effect on electrolyte balance. Hypokalaemia was associated with fluconazole in 3 patients with acute myeloid leukaemia.[1]

1. Kidd D, *et al.* Hypokalaemia in patients with acute myeloid leukaemia after treatment with fluconazole. *Lancet* 1989; **i:** 1017.

Effects on the heart. Prolonged QT interval and torsade de pointes have been reported rarely in patients receiving fluconazole.[1-5]

1. Wassmann S, *et al.* Long QT syndrome and torsade de pointes in a patient receiving fluconazole. *Ann Intern Med* 1999; **131:** 797.
2. Tholakanahalli VN, *et al.* Fluconazole-induced torsade de pointes. *Ann Pharmacother* 2001; **35:** 432–4.
3. Khazan M, Mathis AS. Probable case of torsades de pointes induced by fluconazole. *Pharmacotherapy* 2002; **22:** 1632–7.
4. Pham CP, *et al.* Long QTc interval and torsade de pointes caused by fluconazole. *Ann Pharmacother* 2006; **40:** 1456–61.
5. McMahon JH, Grayson ML. Torsades de pointes in a patient receiving fluconazole for cerebral cryptococcosis. *Am J Health-Syst Pharm* 2008; **65:** 619–23.

Effects on the liver. Although severe hepatic reactions to fluconazole are rare they have been reported, especially in patients with severe underlying diseases or hepatic dysfunction.[1,2] Elevated liver enzymes are commonly found and there have been reports of jaundice.[3,4] Hepatic necrosis has been seen rarely post mortem in patients with severe underlying disease who had received fluconazole. In one such patient, hepatotoxicity was concluded to be dose-dependent.[5]

1. Wells C, Lever AML. Dose-dependent fluconazole hepatotoxicity proven on biopsy and rechallenge. *J Infect* 1992; **24:** 111–12.
2. Jacobson MA, *et al.* Fatal acute hepatic necrosis due to fluconazole. *Am J Med* 1994; **96:** 188–90.
3. Holmes J, Clements D. Jaundice in HIV positive haemophiliac. *Lancet* 1989; **i:** 1027.
4. Franklin IM, *et al.* Fluconazole-induced jaundice. *Lancet* 1990; **336:** 565.
5. Bronstein J-A, *et al.* Fatal acute hepatic necrosis due to dose-dependent fluconazole hepatotoxicity. *Clin Infect Dis* 1997; **25:** 1266–7.

Hypersensitivity. Desensitisation has been successfully carried out in a patient with AIDS who exhibited hypersensitivity to both fluconazole and itraconazole.[1] Gradually increasing oral doses of fluconazole (starting at 5 mg daily) were given over 7 days; thereafter dosage was maintained at 400 mg daily. No adverse reactions were noted during the desensitisation period or in the 3 months up to the publication of the report.

1. Takahashi T, *et al.* Desensitization to fluconazole in an AIDS patient. *Ann Pharmacother* 2001; **35:** 642–3.

Precautions

Fluconazole should be used with caution in patients with impaired hepatic or renal function. Abnormalities in haematological, hepatic, and renal-function tests have been observed in patients with serious underlying diseases such as AIDS or malignancy. Cases of torsade de pointes and QT prolongation have been reported rarely and caution is advised when giving fluconazole to patients with proarrhythmic conditions.

Teratogenicity has occurred in *animals* given high doses of fluconazole and its use is not recommended in pregnancy (see under Pregnancy, below).

Breast feeding. Fluconazole is distributed into breast milk, achieving concentrations similar to those found in maternal plasma,[1] and its use in women who are breast feeding is not recommended by licensed product information.

In one report,[2] no untoward effects, other than a slight increase in lactase dehydrogenase level, were seen in an infant who was exposed to fluconazole in breast milk for 6 weeks.

The American Academy of Pediatrics considers that the use of fluconazole is usually compatible with breast feeding.[3]

1. Force RW. Fluconazole concentrations in breast milk. *Pediatr Infect Dis J* 1995; **14:** 235–6.
2. Bodley V, Powers D. Long-term treatment of a breastfeeding mother with fluconazole-resolved nipple pain caused by yeast: a case study. *J Hum Lact* 1997; **13:** 307–11.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 21/06/05)

Pregnancy. High (toxic) doses of *fluconazole*, *itraconazole*, and *ketoconazole* have been reported to be teratogenic in *rodents.* Although there is little information about the use of these drugs in human pregnancy, there is a report of a woman who took fluconazole 400 mg daily throughout pregnancy and who gave birth to an infant with severe craniofacial and limb abnormalities.[1] The abnormalities resembled those associated with the Antley-Bixler syndrome, a genetic disorder, but a teratogenic effect could not be excluded. Although prescription-event-monitoring studies of fluconazole did not reveal adverse effects on the fetus,[2-4] congenital abnormalities have occurred in infants whose mothers were given high doses of fluconazole for 3 months or more. Data collected by the manufacturer,[5] relating to 198 women exposed to itraconazole during the first trimester of pregnancy, indicated that the malformation rate for both exposed women and matched controls was within the expected baseline risk for the general population. Nevertheless, the manufacturers recommend that fluconazole, itraconazole, and ketoconazole should be avoided during pregnancy.

Licensed product information states that doses of *voriconazole* equivalent to those used therapeutically have been shown to be teratogenic and embryotoxic in *rodents*. It therefore recommends that voriconazole should be avoided during pregnancy and that women of child bearing potential should use effective contraception during treatment. Similar recommendations have been made for *posaconazole*.

Other azole antifungals including butoconazole, clotrimazole, econazole, miconazole, sulconazole, terconazole, and tioconazole are reported to be embryotoxic but not teratogenic in *rodents* given high doses. Many of these drugs are used topically or intravaginally and the systemic absorption from these routes of administration varies. While these drugs may not necessarily be contra-indicated in pregnancy, consideration should be given to these potential risks when choosing antifungal therapy for such patients.

1. Lee BE, *et al.* Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J* 1992; **11:** 1062–4.
2. Rubin PC, *et al.* Fluconazole and pregnancy: results of a prescription event-monitoring study. *Int J Gynecol Obstet* 1992; **37** (suppl): 25–7.
3. Inman W, *et al.* Safety of fluconazole in the treatment of vaginal candidiasis: a prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol* 1994; **46:** 115–18.
4. Sørensen HT, *et al.* Risk of malformations and other outcomes in children exposed to fluconazole in utero. *Br J Clin Pharmacol* 1999; **48:** 234–8.
5. Bar-Oz B, *et al.* Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol* 2000; **183:** 617–20.

Renal impairment. For dose adjustments in renal impairment, see Administration in Renal Impairment, under Uses and Administration, below.

Interactions

In general, fewer interactions are considered to occur with fluconazole than with either itraconazole or ketoconazole.

Use of rifampicin with fluconazole results in reduced plasma concentrations of fluconazole. Use of hydrochlorothiazide and fluconazole has resulted in clinically insignificant increases in plasma-fluconazole concentrations.

Fluconazole may interfere with the metabolism of some other drugs, mainly through inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. This may account for the reported increases in plasma concentrations of bosentan, ciclosporin, midazolam, nevirapine, amitriptyline, nortriptyline, phenytoin, rifabutin, sulfonylurea hypoglycaemics and nateglinide, selective cyclo-oxygenase-2-inhibitors such as celecoxib and parecoxib, tacrolimus, triazolam, warfarin, and zidovudine; fluconazole may inhibit the formation of a toxic metabolite of sulfamethoxazole.

Increases in terfenadine concentrations following high doses of fluconazole have been associated with ECG abnormalities. A similar effect may be anticipated with astemizole. Use of fluconazole with cisapride could result in increased cisapride concentrations and associated toxicity. The use of fluconazole with astemizole, cisapride, or terfenadine should therefore be avoided because of the risk of cardiac arrhythmias. Syncope attributed to increased amitriptyline concentrations has occurred when amitriptyline was given with fluconazole.

Fluconazole may also reduce the clearance of theophylline. The concentration of contraceptive steroids has been reported to be both increased and decreased in patients receiving fluconazole and the efficacy of oral contraceptives may be affected.

For further information on interactions between drugs metabolised by the cytochrome P450 isoenzyme CYP3A and azoles, see under Itraconazole, p.537.

Antineoplastics. For the effect of azole antifungals on *cyclophosphamide* metabolism, see p.703.

Fluoroquinolones. Both *levofloxacin* and fluconazole can cause a prolonged QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; **60:** 2479–83.

Nitrofurans. For a report of pulmonary and hepatic toxicity due to a possible interaction between *nitrofurantoin* and fluconazole, see p.308.

Antimicrobial Action

Fluconazole is a triazole antifungal drug which in sensitive fungi inhibits cytochrome P450-dependent enzymes, resulting in impairment of ergosterol synthesis in fungal cell membranes. It is active against *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton* spp., *Histoplasma capsulatum*, *Microsporum* spp., and *Trichophyton* spp.

Resistance has developed in some *Candida* spp. following long-term prophylaxis with fluconazole, and cross-resistance with other azoles has been reported.

Microbiological interactions. A synergistic antifungal effect was seen *in vitro* with terbinafine and fluconazole against strains

of *Candida albicans*.[1] For effects on the antifungal activity of fluconazole when given with amphotericin B, see p.525.

1. Barchiesi F, *et al.* In vitro activities of terbinafine in combination with fluconazole and itraconazole against isolates of Candida albicans with reduced susceptibility to azoles. *Antimicrob Agents Chemother* 1997; **41:** 1812–14.

Resistance. The emergence of strains of *Candida* spp. resistant to fluconazole has become increasingly important, particularly in immunocompromised patients receiving long-term prophylaxis with fluconazole.[1,2] In addition to resistance in *C. albicans*,[3-5] infections with *C. dubliniensis*,[5] *C. glabrata*, and *C. krusei*, all of which may be less sensitive to fluconazole than *C. albicans*, have been noted in these patients,[6,7] and secondary resistance of *C. glabrata* has been reported during fluconazole therapy.[8,9] Resistance to fluconazole has been reported to occur more frequently than resistance to either ketoconazole or itraconazole and may be related to the widespread use of this drug.[4,7] Cross-resistance with other azoles[10,11] and with amphotericin B[12,13] has been reported.

Fluconazole resistance has also been reported in *Cryptococcus neoformans*[14] and *Histoplasma capsulatum*.[15] Histoplasmosis developed during treatment with fluconazole in a patient with HIV infection.[16] Fluconazole-resistant *C. neoformans* has been isolated from an immunocompetent patient who had not been exposed to azole antifungals previously.[17]

1. Rex JH, *et al.* Resistance of Candida species to fluconazole. *Antimicrob Agents Chemother* 1995; **39:** 1–8.
2. Brion LP, *et al.* Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect* 2007; **54:** 521–9.
3. Sandven P, *et al.* Susceptibilities of Norwegian Candida albicans strains to fluconazole: emergence of resistance. *Antimicrob Agents Chemother* 1993; **37:** 2443–8.
4. Johnson EM, *et al.* Emergence of azole drug resistance in Candida species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidosis. *J Antimicrob Chemother* 1995; **35:** 103–14.
5. Ruhnke M, *et al.* Development of simultaneous resistance to fluconazole in Candida albicans and Candida dubliniensis in a patient with AIDS. *J Antimicrob Chemother* 2000; **46:** 291–5.
6. Price MF, *et al.* Fluconazole susceptibilities of Candida species and distribution of species recovered from blood cultures over a 5-year period. *Antimicrob Agents Chemother* 1994; **38:** 1422–4.
7. Odds FC. Resistance of yeasts to azole-derivative antifungals. *J Antimicrob Chemother* 1993; **31:** 463–71.
8. Hitchcock CA, *et al.* Fluconazole resistance in Candida glabrata. *Antimicrob Agents Chemother* 1993; **37:** 1962–5.
9. Miyazaki H, *et al.* Fluconazole resistance associated with drug efflux and increased transcription of a drug transporter gene, PDH1, in Candida glabrata. *Antimicrob Agents Chemother* 1998; **42:** 1695–1701.
10. Martinez-Suarez JV, Rodriguez-Tudela JL. Patterns of in vitro activity of itraconazole and imidazole antifungal agents against Candida albicans with decreased susceptibility to fluconazole from Spain. *Antimicrob Agents Chemother* 1995; **39:** 1512–16.
11. Goldman M, *et al.* Does long-term itraconazole prophylaxis result in in vitro azole resistance in mucosal Candida albicans isolates from persons with advanced human immunodeficiency virus infection? *Antimicrob Agents Chemother* 2000; **44:** 1585–7.
12. Kelly SL, *et al.* Resistance to fluconazole and amphotericin in Candida albicans from AIDS patients. *Lancet* 1996; **348:** 1523–4.
13. Nolte FS, *et al.* Isolation and characterization of fluconazole- and amphotericin B-resistant Candida albicans from blood of two patients with leukemia. *Antimicrob Agents Chemother* 1997; **41:** 196–9.
14. Venkateswarlu K, *et al.* Fluconazole tolerance in clinical isolates of Cryptococcus neoformans. *Antimicrob Agents Chemother* 1997; **41:** 748–51.
15. Wheat J, *et al.* Hypothesis on the mechanism of resistance to fluconazole in Histoplasma capsulatum. *Antimicrob Agents Chemother* 1997; **41:** 410–14.
16. Pottage JC, Sha BE. Development of histoplasmosis via human immunodeficiency virus infected patient receiving fluconazole. *J Infect Dis* 1991; **164:** 622–3.
17. Omi-Wasserlauf R, *et al.* Fluconazole-resistant Cryptococcus neoformans isolated from an immunocompetent patient without prior exposure to fluconazole. *Clin Infect Dis* 1999; **29:** 1592–3.

Pharmacokinetics

Fluconazole is well absorbed after oral doses, bioavailability from the oral route being 90% or more of that from the intravenous route. Mean peak plasma concentrations of 6.72 micrograms/mL have been reported in healthy subjects after a 400-mg oral dose. Peak concentrations are reached within 1 to 2 hours of oral doses. Plasma concentrations are proportional to the dose over a range of 50 to 400 mg. Multiple dosing leads to increases in peak plasma concentrations; steady-state concentrations are reached in 5 to 10 days but may be attained on day 2 if a loading dose is given.

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

About 80% of a dose is excreted unchanged in the urine and about 11% as metabolites. The elimination half-life of fluconazole is about 30 hours and is increased in patients with renal impairment. Fluconazole is removed by dialysis.

◊ Reviews.

1. Debruyne D, Ryckelynek J-P. Clinical pharmacokinetics of fluconazole. *Clin Pharmacokinet* 1993; **24:** 10–27.
2. Debruyne D. Clinical pharmacokinetics of fluconazole in superficial and systemic mycoses. *Clin Pharmacokinet* 1997; **33:** 52–77.
3. Pittrow L, Penk A. Special pharmacokinetics of fluconazole in septic, obese and burn patients. *Mycoses* 1999; **42** (suppl 2): 87–90.
4. Silling G. Fluconazole: optimized antifungal therapy based on pharmacokinetics. *Mycoses* 2002; **45** (suppl 3): 39–41.

Burns. The mean half-life of fluconazole was decreased to 24.4 hours in 9 patients with burns.[1] Fluconazole clearance was 27.5 mL/minute, which was 30% higher than that reported in healthy subjects.

1. Boucher BA, *et al.* Fluconazole pharmacokinetics in burn patients. *Antimicrob Agents Chemother* 1998; **42:** 930–3.

Children and neonates. References.

1. Saxén H, *et al.* Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther* 1993; **54:** 269–77.
2. Nahata MC, Brady MT. Pharmacokinetics of fluconazole after oral administration in children with human immunodeficiency virus infection. *Eur J Clin Pharmacol* 1995; **48:** 291–3.

Distribution. Salivary concentrations of fluconazole after oral doses should be adequate for the treatment of oropharyngeal and oesophageal candidiasis[1,2] even in patients with AIDS who may have decreased salivation.[3] Treatment failures are more likely to be due to inadequate dosage or resistant organisms than to decreased salivary secretion.[3]

Pharmacologically active concentrations of fluconazole have been detected in scalp hair[4] and nails[5] after oral treatment with conventional daily doses and with once-weekly dosage.

1. Force RW, Nahata MC. Salivary concentrations of ketoconazole and fluconazole: implications for drug efficacy in oropharyngeal and esophageal candidiasis. *Ann Pharmacother* 1995; **29:** 10–15.
2. Koks CHW, *et al.* Pharmacokinetics of fluconazole in saliva and plasma after administration of an oral suspension and capsules. *Antimicrob Agents Chemother* 1996; **40:** 1935–7.
3. Garcia-Hermoso D, *et al.* Fluconazole concentrations in saliva from AIDS patients with oropharyngeal candidosis refractory to treatment with fluconazole. *Antimicrob Agents Chemother* 1995; **39:** 656–60.
4. Yeates R, *et al.* Accumulation of fluconazole in scalp hair. *J Clin Pharmacol* 1998; **38:** 138–43.
5. Faergemann J. Pharmacokinetics of fluconazole in skin and nails. *J Am Acad Dermatol* 1999; **40** (suppl): S14–S20.

HIV-infected patients. Plasma clearance of fluconazole may be lower in patients with HIV infection than in immunocompetent patients, and the half-life may be prolonged.[1,2]

1. Tett S, *et al.* Pharmacokinetics and bioavailability of fluconazole in two groups of males with human immunodeficiency virus (HIV) infection compared with those in a group of males without HIV infection. *Antimicrob Agents Chemother* 1995; **39:** 1835–41.
2. McLachlan AJ, Tett SE. Pharmacokinetics of fluconazole in people with HIV infection: a population analysis. *Br J Clin Pharmacol* 1996; **41:** 291–8.

Uses and Administration

Fluconazole is a triazole antifungal used for superficial mucosal (oropharyngeal, oesophageal, or vaginal) candidiasis and for fungal skin infections. It is also given for systemic infections including systemic candidiasis, coccidioidomycosis, and cryptococcosis, and has been tried in blastomycosis, histoplasmosis, and sporotrichosis. The place of fluconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p.517.

Fluconazole is given by mouth or intravenous infusion in similar doses. For intravenous infusion it is given as a solution containing 2 mg/mL at a rate of 5 to 10 mL/minute (300 to 600 mL/hour). In the USA, a maximum infusion rate of 100 mL/hour is recommended.

For **superficial mucosal candidiasis** (other than genital candidiasis), the usual dose of fluconazole in the UK is 50 mg daily by mouth, although 100 mg daily may be given if necessary. Treatment usually continues for 7 to 14 days in *oropharyngeal* candidiasis (except in severely immunocompromised patients), for 14 days in *atrophic oral candidiasis* associated with dentures, and for 14 to 30 days in other mucosal candidal infections including *oesophagitis*.

Higher doses are recommended in the USA where an initial dose of fluconazole 200 mg is followed by 100 mg daily and where the minimum treatment period is 14 days for oropharyngeal infection, or a minimum of 21 days and at least 14 days after resolution of symptoms for oesophageal infections; doses of up to 400 mg daily may be used for oesophageal candidiasis if necessary.

Fluconazole 150 mg as a single oral dose may be used for **genital candidiasis** (vaginal candidiasis or candidal balanitis).

Dermatophytosis, pityriasis versicolor, and *Candida* **infections of the skin** may be treated with fluconazole 50 mg daily by mouth for up to 6 weeks.

Systemic candidiasis, **cryptococcal meningitis**, and other **cryptococcal infections** may be treated with fluconazole orally or by intravenous infusion; the initial dose is 400 mg followed by 200 to 400 mg daily. Duration of therapy is based on clinical and mycological response, but is usually at least 6 to 8 weeks in cryptococcal meningitis; in the USA, treatment for 10 to 12 weeks after the CSF cultures become negative is recommended. Fluconazole may also be used in daily doses of 100 to 200 mg orally or intravenously to prevent relapse after a primary course of antifungal treatment for acute cryptococcal meningitis in patients with AIDS.

In *immunocompromised patients* at risk of fungal infections, fluconazole may be given **prophylactically** in a dose of 50 to 400 mg daily orally or by intravenous infusion, although long-term prophylaxis has been associated with the emergence of resistant organisms (see under Intermittent Doses, below).

Doses for **children** over 4 weeks of age are 3 mg/kg daily for superficial infections (a loading dose of 6 mg/kg may be used on the first day if necessary), and 6 to 12 mg/kg daily for systemic infections. For prophylaxis in immunocompromised children, a dose of 3 to 12 mg/kg daily may be given. For infants under 2 weeks of age, all these doses should be given once every 72 hours; for those aged between 2 and 4 weeks, the doses should be given every 48 hours. A maximum dose of 400 mg daily should not be exceeded in children, or 12 mg/kg at appropriate intervals in infants.

Dosage may need to be reduced in patients with **renal impairment** (see below).

◊ Reviews.

1. Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial and systemic mycoses. *Drugs* 1990; **39:** 877–916. Correction. *ibid.* **40:** 862.
2. Kowalsky SF, Dixon DM. Fluconazole: a new antifungal agent. *Clin Pharm* 1991; **10:** 179–94.
3. Goa KL, Barradell LB. Fluconazole: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in major superficial and systemic mycoses in immunocompromised patients. *Drugs* 1995; **50:** 658–90.
4. Charlier C, *et al.* Fluconazole for the management of invasive candidiasis: where do we stand after 15 years? *J Antimicrob Chemother* 2006; **57:** 384–410.

Administration. *HIGH DOSES.* Doses higher than those recommended by licensed product information for fluconazole have been tried in patients with life-threatening infections caused by *Candida* spp., *Cryptococcus neoformans*, and *Coccidioides immitis*. Dose finding studies have found daily doses of 800 to 1000 mg of fluconazole to be effective and well tolerated.[1-3] In a study of 11 HIV-infected patients who received fluconazole 800 to 1000 mg daily intravenously for 3 weeks then orally until the CSF culture became negative, 6 patients had responded at 10 weeks and another 2 improved clinically.[1] Daily doses of up to 800 mg have been used in blastomycosis[2] and coccidioidomycosis,[3] and doses of 10 mg/kg daily have been tried in disseminated candidiasis.[4]

1. Menichetti F, *et al.* High-dose fluconazole therapy for cryptococcal meningitis in patients with AIDS. *Clin Infect Dis* 1996; **22:** 838–40.
2. Pappas PG, *et al.* Treatment of blastomycosis with higher doses of fluconazole. *Clin Infect Dis* 1997; **25:** 200–5.
3. Galgiani JN, *et al.* Infectious Diseases Society of America. Practice guidelines for the treatment of coccidioidomycosis. *Clin Infect Dis* 2000; **30:** 658–61. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/313747 (accessed 18/07/08)
4. Graninger W, *et al.* Treatment of Candida albicans fungaemia with fluconazole. *J Infect* 1993; **26:** 133–46.

INTERMITTENT DOSES. Concern has been expressed about the increasingly widespread use of fluconazole[1] and, in particular, about the impact of continuous fluconazole therapy in immunocompromised patients on the development of resistance (see under Antimicrobial Action, above). Nevertheless, fluconazole remains popular for primary and secondary prophylaxis.

Some investigators have suggested the use of intermittent doses[2,3] although this could further increase the risk of infections with resistant organisms.

Once-weekly treatment with fluconazole has been tried in onychomycosis[4] and tinea capitis.[5]

1. Mangino JE, *et al.* When to use fluconazole. *Lancet* 1995; **345:** 6–7.
2. Singh N, *et al.* Low-dose fluconazole as primary prophylaxis for cryptococcal infection in AIDS patients with CD4 cell counts of ≤ 100/mm : demonstration of efficacy in a prospective, multicenter trial. *Clin Infect Dis* 1996; **23:** 1282–6.
3. Schuman P, *et al.* Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997; **126:** 689–96.
4. Scher RK, *et al.* Once-weekly fluconazole (150 mg, 300 mg, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38:** S77–S86.
5. Gupta AK, *et al.* Once weekly fluconazole is effective in children in the treatment of tinea capitis: a prospective, multicentre study. *Br J Dermatol* 2000; **142:** 965–8.

Administration in renal impairment. Patients with renal impairment may require dosage reduction. Normal loading or initial doses of fluconazole should be given on the first day of treatment and subsequent doses should be adjusted according to creatinine clearance (CC):

- CC more than 50 mL/minute: 100% of the standard recommended dose
- CC less than 50 mL/minute and not receiving dialysis: 50% of the standard recommended dose
- patients on regular haemodialysis: 100% of the standard recommended dose after each dialysis session

No dosage adjustment is needed in patients with renal impairment given single-dose therapy.

Leishmaniasis. Fluconazole has been tried in the treatment of cutaneous leishmaniasis (p.824) caused by *Leishmania major*. In a randomised, double-blind, placebo-controlled study,[1] 80 patients received a six-week course of oral fluconazole 200 mg daily, of whom 63 had complete healing of lesions after 3 months, compared with 22 of 65 patients who received placebo. However, others[2] have reported a response rate not significantly different from placebo.

1. Alrajhi AA, *et al.* Fluconazole for the treatment of cutaneous leishmaniasis caused by Leishmania major. *N Engl J Med* 2002; **346:** 891–5.
2. Morizot G, *et al.* Healing of Old World cutaneous leishmaniasis in travelers treated with fluconazole: drug effect or spontaneous evolution? *Am J Trop Med Hyg* 2007; **76:** 48–52. Correction. *ibid.*; 791.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Candimicol; Damicol; Femixol; Fluconovag; Fluzol; Fungocina; Fungototal; Honguil Plus; Klonazol; Micolis Novo; Mutum; Naxo C; Nifurtox; Niofen; Periplum; Ponaris; Proseda F; Triflucan; ***Austral.:*** Diflucan; Dizole; Fluzole; Ozole; ***Austria:*** Diflucan; Diflucohexal; Difluzol; Fluconabene; Flucosept; Flucozal; Fungata; ***Belg.:*** Diflucan; Fungimed; ***Braz.:*** Candix; Candizol; Celozol†; Farmazol†; Floltec; Flucanil; Flucanol†; Flucazol; Flucodan; Flucoltrix†; Flucomed; Fluconal; Fluconax†; Fluconeo; Flucozen; Flucozix†; Flunal†; Flunazol†; Flutec†; Fungnon; Glyflucan; Helmicin; Monipax†; Pantec; Pronazol†; Riconazol; Triazol; Unizol; Zelix; Zolanix; Zolmic; Zolstatin†; Zoltec; Zoltren; ***Canad.:*** Diflucan; ***Chile:*** Diflucan; Felsol; Flucoxan; Fluctin; Fungimax; Ibarin; Micofin†; Microvaccin; Plusgin; Tavor; ***Cz.:*** Diflazon; Diflucan; Fluco; Forcan; Mycomax; Mycosyst; Mykohexal; ***Denm.:*** Conasol; Diflucan; Fungal†; ***Fin.:*** Diflucan; ***Fr.:*** Beagyne; Triflucan; ***Ger.:*** Canex; Diflucan; Fluc†; Flucobeta; Flucoderm; FlucoLich; Flunazul; Fungata; ***Gr.:*** Azoflu; Farviron; Figalol; Flucocaps; Flucodrug; Fluconapen; Flusenil; Funadel; Fungo; Fungustatin; Fungusteril; Fuxilidin; Gynosant; Hadlinol; Medoflucon; Mycazole; Rifagen; Stabilanol; Tierlite; Varmec; Zidonil; ***Hong Kong:*** Diflucan; Fluconic; Flucozal; Fludicon; Forcan; Lucon; Nofung; Stalene; ***Hung.:*** Dermyc; Diflazon†; Diflucan; Flucohexal; Fluconic; Mycosyst; Nofung; ***India:*** Flumyc†; Fluzon; Forcan; Logican; Nipcan; Syscan; ***Indon.:*** Cancid; Candizol; Cryptal; Diflucan; Flucess; Fluconal; Govazol; Zemyc; ***Irl.:*** Diflazole; Diflucan; Flucandid; Flucol; ***Israel:*** Diflucan; Flucanol; Trican; Triflucan; ***Ital.:*** Biozolene†; Diflucan; Elazor; ***Jpn:*** Diflucan†; ***Malaysia:*** Biozole; Diflucan; Fluconic; Flugal; Fukole; Medoflucon; Stalene; Zolstan; ***Mex.:*** Afungil; Bioxel; Candizol; Diflucan; Difusel; Fectrin; Flucoxan; Fludisol; Fluhexal; Flukezol; Fluxes; Fluxicap; Fluzor; Funser; Lanfluzol; Neofomiral; Ongicil; Oxifungol; Solarisol; Terplex; Zoldicam; ***Neth.:*** Diflucan; ***Norw.:*** Diflucan; ***NZ:*** Canesten Fluconazole; Diflucan; Flucazole; ***Philipp.:*** Diflucan; Funzela; Syscan; ***Pol.:*** Diflucan; Flucofast; Flumycon; Mycomax; Mycosyst; ***Port.:*** Azoflune; Diflucan; Fludocel; Maxflin; Reforce; Supremase; ***Rus.:*** Diflazon (Дифлазон); Diflucan (Дифлюкан); Flucostat (Флюкостат); Flucozan (Флукозан)†; Flumicon (Флюмикон); Fungolon (Фунголон); Funzole (Фунзол); Medoflucon (Медофлюкон); Mycoflucan (Микофлюкан); Mycomax (Микомакс); Mycosyst (Микосист); Syscan (Цискан); ***S.Afr.:*** Diflucan; Difluzole; Fluconic; Fluzol; ***Singapore:*** Diflucan; Medoflucon; Mycorest; Omastin; Stalene; ***Spain:*** Diflucan; Lavisa; Loitin; Solacap†; ***Swed.:*** Diflucan; ***Switz.:*** Diflucan; Flucazol; Fluconax; Flunizol; Mykantol; ***Thai.:*** Biozole; Diflucan; Flucozole; Fludizol; Flunco; Funa; Kyrin; Stalene; ***Turk.:*** Biocanol; Candidin; Flucan; Fluzole; Fungan; Kandizol; Lumen; Triflucan; Trizol; Zolax; ***UK:*** Canesten Oral; Diflucan; ***USA:*** Diflucan; ***Venez.:*** Aflumicort; Albesin; Diflucan; Flucess; Flucon; Flunal; Fluval; Fugin; Fungomax; Funizol; Micoflux; Mutum; Zolstan†.

Multi-ingredient: ***Arg.:*** Gynerium UD; ***Austral.:*** Canesoral Duo; ***India:*** Forcan TZ; Orflaz Kit; Safkit; ***Mex.:*** Afumix.

Flucytosine *(BAN, USAN, rINN)*

5-FC; Flucitosina; Flucitozin; Flucitozinas; Flucytosin; Flucytosinum; Flucytozyna; Flusitozin; Flusytosiini; Ro-2-9915. 5-Fluorocytosine; 4-Amino-5-fluoropyrimidin-2(1*H*)-one.

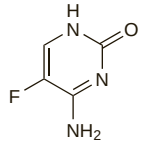
Флуцитозин

$C_4H_4FN_3O$ = 129.1.

CAS — 2022-85-7.

ATC — D01AE21; J02AX01.

ATC Vet — QD01AE21; QJ02AX01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Flucytosine). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in dehydrated alcohol. Protect from light.

USP 31 (Flucytosine). A white to off-white crystalline powder, odourless or with a slight odour. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. A solution of flucytosine for intravenous infusion should be stored between 18° and 25°. Precipitation may occur at lower temperatures and decomposition, with the formation of fluorouracil, at higher temperatures.

Adverse Effects

Adverse effects of flucytosine include nausea, vomiting, diarrhoea, and skin rashes. Less frequently reported adverse effects include confusion, hallucinations, convulsions, headache, sedation, and vertigo, and also allergic reactions, toxic epidermal necrolysis, and cardiotoxicity. Alterations in liver function tests are generally dose-related and reversible; hepatotoxicity may also occur. Hypokalaemia may occur. There have been a few reports of peripheral neuropathy.

Bone-marrow depression, especially leucopenia and thrombocytopenia, is associated with blood concentrations of flucytosine greater than 100 micrograms/mL, with concurrent use of amphotericin B, and with renal impairment. Fatal agranulocytosis and aplastic anaemia have been reported.

Effects on the blood. Bone marrow toxicity associated with flucytosine has been attributed to its conversion to fluorouracil, possibly by intestinal flora.[1] A pilot study[2] of 6 patients given intravenous flucytosine found that the amounts of fluorouracil in serum samples were undetectable, whereas flucytosine could be detected in the samples. This might be because intravenous dosage did not allow the conversion of flucytosine to fluorouracil by intestinal microflora. However, one patient still developed thrombocytopenia and another leucocytopenia and the authors hypothesised that toxicity might be due to flucytosine and not the metabolite.

1. Pirmohamed M, *et al.* The role of active metabolites in drug toxicity. *Drug Safety* 1994; **11:** 114–44.
2. Vermes A, *et al.* 5-fluorocytosine-related bone-marrow depression and conversion to fluorouracil: a pilot study. *Fundam Clin Pharmacol* 2002; **16:** 39–47.

Precautions

Flucytosine should be given with great care to patients with renal impairment, or with blood disorders or bone marrow depression. Renal and hepatic function and blood counts should be monitored during therapy (at least weekly in patients with renal impairment or blood disorders). In patients with renal impairment, doses should be reduced and trough blood concentrations of flucytosine should be checked regularly from blood samples taken just before an injection of flucytosine (see under Uses, below). Care should be taken in patients given radiation therapy or other drugs which depress bone marrow.

Flucytosine is teratogenic in *rats*.

AIDS. Frequent bone marrow toxicity has been reported in patients with AIDS during flucytosine therapy.[1] However, in a study in 381 patients, no additional haematotoxicity was reported in patients given amphotericin B plus flucytosine compared with those given amphotericin B alone.[2] The toxicity could be minimised by monitoring serum concentrations[3] and the British Society for Antimicrobial Chemotherapy has suggested that these should be maintained within 25 to 50 micrograms/mL in patients with AIDS.[4]

1. Chuck SL, Sande MA. Infections with Cryptococcus neoformans in the acquired immunodeficiency syndrome. *N Engl J Med* 1989; **321:** 794–9.
2. van der Horst CM, *et al.* Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med* 1997; **337:** 15–21.
3. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35:** 241–4.
4. British Society for Antimicrobial Chemotherapy Working Party. Antifungal chemotherapy in patients with acquired immunodeficiency syndrome. *Lancet* 1992; **340:** 648–51.

Pregnancy. Teratogenicity has been reported in some *animal* models and licensed product information recommends that flucytosine should only be used if the benefit justifies that possible risk to the fetus. The congenital defects are thought to be as a result of the conversion of flucytosine to fluorouracil by the intestinal microflora. However, there are some case reports of pregnant patients receiving flucytosine (with or without amphotericin B) in the second[1-4] and third[5] trimesters with no reports of abnormalities in the infants.

1. Philpot CR, Lo D. Cryptococcal meningitis in pregnancy. *Med J Aust* 1972; **2:** 1005–7.
2. Schönebeck J, Segerbrand E. Candida albicans septicaemia during first half of pregnancy successfully treated with 5-fluorocytosine. *BMJ* 1973; **4:** 337–8.
3. Curole DN. Cryptococcal meningitis in pregnancy. *J Reprod Med* 1981; **26:** 317–19.
4. Chotmongkol V, Siricharoensang S. Cryptococcal meningitis in pregnancy: a case report. *J Med Assoc Thai* 1991; **74:** 421–2.
5. Chen C-P, Wang K-G. Cryptococcal meningitis in pregnancy. *Am J Perinatol* 1996; **13:** 35–6.

Interactions

Flucytosine is commonly used with amphotericin B. Amphotericin B can cause a deterioration in renal function, which can result in raised flucytosine blood concentrations and increased toxicity. However, the two drugs are generally regarded as having synergistic antifungal activity. Cytarabine has been claimed to reduce blood concentrations of flucytosine and to antagonise its antifungal activity, although the evidence is limited.

Antimicrobial Action

Flucytosine is a fluorinated pyrimidine antifungal. In susceptible fungi it is converted by cytosine deaminase to fluorouracil which is then incorporated in place of uracil into fungal RNA and disrupts protein synthesis. The activity of thymidilate synthetase is also inhibited and this effect interferes with fungal DNA synthesis.

Flucytosine is active against *Candida* spp., *Cryptococcus neoformans*, *Cladosporium* spp., and *Fonsecaea* spp. Some *Aspergillus* spp. have also been reported to be sensitive. There is synergy between flucytosine and amphotericin B against *Candida* spp. and *Cryptococcus neoformans*.

There is a high incidence of primary resistance to flucytosine among isolates of *Candida* spp. and *Cryptococcus neoformans*. Resistance also develops during treatment with flucytosine and has been reported rarely from combination therapy with flucytosine and amphotericin B.

Pharmacokinetics

Flucytosine is absorbed rapidly and almost completely from the gastrointestinal tract. Bioavailability is 78 to 89%. After oral doses of 37.5 mg/kg every 6 hours, peak plasma concentrations of 70 to 80 micrograms/mL have been achieved within 2 hours; similar concentrations have been achieved but more rapidly, after an intravenous dose. The plasma-flucytosine concentration for optimum response is 25 to 50 micrograms/mL. Flucytosine is widely distributed through the body tissues and fluids; concentrations in the CSF are 65 to 90% of those in serum. About 2 to 4% of flucytosine is protein bound.

About 90% of a dose is excreted unchanged by glomerular filtration; a small amount of flucytosine may be metabolised to fluorouracil. The small amount of an oral dose of flucytosine not absorbed from the gastrointestinal tract is eliminated unchanged in the faeces. The elimination half-life is 2.5 to 6 hours in pa-