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.

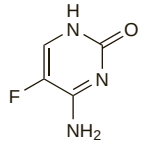
Флуцитозин

$C_4H_4FN_3O$ = 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-

tients with normal renal function but increases with decreasing renal function. Flucytosine is removed by haemodialysis or peritoneal dialysis.

◊ References[1-3] to the pharmacokinetics of flucytosine. A study[3] reviewing flucytosine concentrations in serum, blood, or plasma from 233 patients, including 33 neonates, found that they were within the therapeutic range in only about 20% of cases; of the remainder, 40% were low (5% undetectable) and 40% were excessive (potentially toxic in about 10% of the samples). The results emphasised the importance of therapeutic drug monitoring.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of systemic antifungal agents. *Clin Pharmacokinet* 1983; **8:** 17–42.
2. Baley JE, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990; **116:** 791–7.
3. Pasqualotto AC, *et al.* Flucytosine therapeutic monitoring: 15 years experience from the UK. *J Antimicrob Chemother* 2007; **59:** 791–3.

Uses and Administration

Flucytosine is a fluorinated pyrimidine antifungal used in the treatment of systemic fungal infections, the treatments for which are discussed under Choice of Antifungal, p.517. It is mainly used with amphotericin B or fluconazole in the treatment of severe systemic candidiasis and cryptococcal meningitis. It has also been tried in other infections due to susceptible fungi including chromoblastomycosis.

Flucytosine is given by *intravenous infusion* as a 1% solution over 20 to 40 minutes. The usual dose is 200 mg/kg daily in 4 divided doses; a dose of 100 to 150 mg/kg daily may be sufficient in some patients. Dosage should be adjusted to produce trough plasma concentrations of 25 to 50 micrograms/mL. This is particularly important in patients with AIDS who are at increased risk of bone marrow toxicity. Parenteral treatment is rarely given for more than 7 days, except for cryptococcal meningitis when it is continued for at least 4 months. For intravenous doses to be used in patients with renal impairment, see below.

Flucytosine is given *orally* in usual doses of 50 to 150 mg/kg daily in 4 divided doses. Again, blood concentrations should be monitored and dosage adjusted in patients with renal impairment to avoid accumulation of the drug (see below).

Flucytosine has been used *topically* for azole-refractory vaginitis caused by *Candida* spp., but such use may increase problems of resistance.

◊ Reviews.

1. Viviani MA. Flucytosine—what is its future? *J Antimicrob Chemother* 1995; **35:** 241–4.
2. Summers KK, *et al.* Therapeutic drug monitoring of systemic antifungal therapy. *J Antimicrob Chemother* 1997; **40:** 753–64.
3. Vermes A, *et al.* Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. *J Antimicrob Chemother* 2000; **46:** 171–9.

Administration in renal impairment. Flucytosine is mainly excreted by the kidneys and the dose must be adjusted in patients with renal impairment.

Dose intervals for intravenous flucytosine should be adjusted according to creatinine clearance (CC):

For intravenous use,

- CC 20 to 40 mL/minute: 50 mg/kg every 12 hours
- CC 10 to 20 mL/minute: 50 mg/kg every 24 hours
- CC less than 10 mL/minute: 50 mg/kg then further doses should be based on plasma concentrations which should not exceed 80 micrograms/mL

Initial oral doses should be at the lower end of the recommended range (see above) and dosage should be adjusted subsequently to avoid accumulation.

Preparations

BP 2008: Flucytosine Tablets;
USP 31: Flucytosine Capsules; Flucytosine Oral Suspension.

Proprietary Preparations (details are given in Part 3)

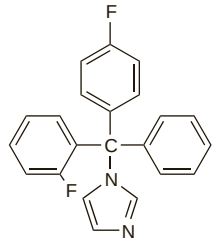
Arg.: Ancotil; ***Austral.:*** Ancotil; ***Austria:*** Ancotil; ***Denm.:*** Ancotil; ***Fr.:*** Ancotil; ***Ger.:*** Ancotil; ***Gr.:*** Ancotil; ***Hong Kong:*** Ancotil; ***Irl.:*** Ancotil; ***Ital.:*** Ancotil; ***Malaysia:*** Ancotil†; ***Neth.:*** Ancotil; ***NZ:*** Alcobon†; Ancotil; ***Pol.:*** Ancotil; ***Rus.:*** Ancotyl (Анкотил); ***Singapore:*** Ancotil†; ***Swed.:*** Ancotil; ***Switz.:*** Ancotil; ***UK:*** Ancotil; ***USA:*** Ancobon.

Flutrimazole *(BAN, rINN)*

Flutrimatsoli; Flutrimazol; Flutrimazolas; Flutrimazolum; UR-4056. 1-[*o*-Fluoro-α-(*p*-fluorophenyl)-α-phenylbenzyl]imidazole; (*RS*)-1-(2,4′-Difluorotrityl)imidazole.

Флутримазол

$C_{22}H_{16}F_2N_2$ = 346.4.
CAS — 119006-77-8.
ATC — D01AC16; G01AF18.
ATC Vet — QD01AC16; QG01AF18.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Flutrimazole). A white or almost white powder. Practically insoluble in water; soluble in methyl alcohol; freely soluble in tetrahydrofuran. Protect from light.

Profile

Flutrimazole is an imidazole antifungal used topically as a 1% cream, gel, powder, or solution in the treatment of superficial fungal infections.

For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Preparations

Proprietary Preparations (details are given in Part 3)

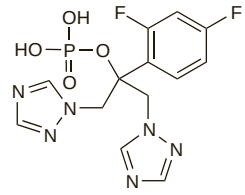
Arg.: Flusporan†; ***Austria:*** Micetal; ***Braz.:*** Micetal; ***Chile:*** Micetal; ***Cz.:*** Micetal; ***Gr.:*** Topiderm; ***Hung.:*** Micetal; ***Ital.:*** Micetal; ***Mex.:*** Micetal; ***Pol.:*** Micetal; ***Port.:*** Flutrim; ***Spain:*** Flusporan; Funcenal; Micetal.

Fosfluconazole *(BAN, rINN)*

Fosfluconazol; Fosfluconazolum; UK-292663. 1-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-1-[(1*H*-1,2,4-triazol-1-yl)methyl]ethyl dihydrogen phosphate.

Фосфлуконазол

$C_{13}H_{13}F_2N_6O_4P$ = 386.3.
CAS — 194798-83-9.



Profile

Fosfluconazole is a phosphate prodrug of fluconazole that is used for the treatment of systemic fungal infections, including oral candidiasis and recurrent cryptococcal meningitis in AIDS patients.

Preparations

Proprietary Preparations (details are given in Part 3)

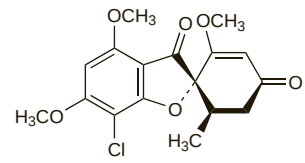
Jpn: Prodif.

Griseofulvin *(BAN, rINN)*

Curling Factor; Griseofulviini; Griseofulvina; Griséofulvine; Griseofulvinum; Grizeofulvin; Grizeofulvinas; Gryzeofulwina. (2*S*,4′*R*)-7-Chloro-2′,4,6-trimethoxy-4′-methylspiro[benzofuran-2(3*H*),3′-cyclohexene]-3,6′-dione.

Гризеофульвин

$C_{17}H_{17}ClO_6$ = 352.8.
CAS — 126-07-8.
ATC — D01AA08; D01BA01.
ATC Vet — QD01AA08; QD01BA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Griseofulvin). An antifungal substance produced by the growth of certain strains of *Penicillium griseofulvum*, or by any other means. It is a white or yellowish-white powder. The particles of the powder are generally up to 5 micrometres in maximum dimension, though larger particles, which may occasionally exceed 30 micrometres, may be present. It contains 97 to 102% of $C_{17}H_{17}ClO_6$, calculated on the dried substance.
Practically insoluble in water; slightly soluble in dehydrated alcohol and in methyl alcohol; freely soluble in dimethylformamide and in tetrachloroethane.
USP 31 (Griseofulvin). A white to creamy-white, odourless powder, in which particles of the order of 4 micrometres in diameter predominate. It has a potency of not less than 900 micrograms of $C_{17}H_{17}ClO_6$ per mg. Very slightly soluble in water; sparingly soluble in alcohol; soluble in acetone, in chloroform, and in dimethylformamide. Store in airtight containers.

Adverse Effects

Adverse effects are usually mild and transient and consist of headache, skin rashes and urticaria, dry mouth, an altered sensation of taste, and gastrointestinal disturbances. Angioedema, erythema multiforme, toxic epidermal necrolysis, proteinuria, leucopenia and other blood dyscrasias, oral candidiasis, peripheral neuropathy, photosensitisation, and severe headache have been reported occasionally. Depression, confusion, dizziness, impaired coordination, insomnia, and fatigue have also been reported. Griseofulvin may precipitate or aggravate systemic lupus erythematosus.

There have been a few reports of hepatotoxicity attributed to griseofulvin.

Effects on the skin. Fatal toxic epidermal necrolysis in a 19-year-old woman[1] was attributed to griseofulvin that she had taken for 6 days; she had also taken metronidazole for 1 day. There are also reports[2,3] of erythema multiforme in 4 patients occurring within 10 days of starting griseofulvin. The precipitation or aggravation of systemic lupus erythematosus is a known complication of griseofulvin. Most cases are said to be characterised by prominent skin manifestations and absence of renal disease although the nephrotic syndrome has been described[4] in a 16-year-old male after 2 single doses of griseofulvin taken 3 weeks apart.

1. Mion G, *et al.* Fatal toxic epidermal necrolysis after griseofulvin. *Lancet* 1989; **ii:** 1331.
2. Rustin MHA, *et al.* Erythema multiforme due to griseofulvin. *Br J Dermatol* 1989; **120:** 455–8.
3. Thami GP, *et al.* Erythema multiforme due to griseofulvin with positive re-exposure test. *Dermatology* 2001; **203:** 84–5.
4. Bonilla-Felix M, *et al.* Nephrotic syndrome related to systemic lupus erythematosus after griseofulvin therapy. *Pediatr Nephrol* 1995; **9:** 478–9.

Hypersensitivity. A serum sickness-like reaction has been reported in a 5-year-old child being treated for tinea capitis with griseofulvin.[1] About 3 weeks after starting treatment the child developed fever, rash on his legs and back, swelling of his toes and fingers, and leg pain. Symptoms resolved after griseofulvin was stopped.

1. Colton RL, *et al.* Serum sickness-like reaction associated with griseofulvin. *Ann Pharmacother* 2004; **38:** 609–11.

Precautions

Griseofulvin is contra-indicated in patients with severe liver disease or systemic lupus erythematosus.

Griseofulvin is embryotoxic and teratogenic in *rats* and there have been isolated cases of conjoined twins after its use during the first trimester of pregnancy. It is therefore contra-indicated in pregnancy and women should not become pregnant during, or within 1 month of stopping therapy. Griseofulvin may reduce the effectiveness of oral contraceptives and additional contraceptive precautions should be used during treatment. Data from *in-vitro* and *in-vivo* studies using mammalian cells, which showed aneuploidy, have led to the warning that men taking griseofulvin should not father children within 6 months of treatment.