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)

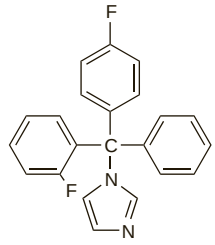
Arg.: Ancotil; ***Austral.:*** Ancotil; ***Austria:*** Ancotil; ***Denm.:*** Ancotil; ***Fr.:*** Ancotil; ***Ger.:*** Ancotil; ***Gr.:*** Ancotil; ***Hong Kong:*** Ancotil; ***Irl.:*** Ancotil; ***Ital.:*** Ancotil; ***Malaysia:*** Ancotil†; ***Neth.:*** Ancotil; ***NZ:*** Alcobon†; Ancotil; ***Pol.:*** 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)

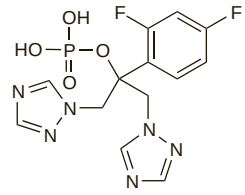
Arg.: Flusporan†; ***Austria:*** Micetal; ***Braz.:*** Micetal; ***Chile:*** Micetal; ***Cz.:*** Micetal; ***Gr.:*** Topiderm; ***Hung.:*** Micetal; ***Ital.:*** Micetal; ***Mex.:*** Micetal; ***Pol.:*** Micetal; ***Port.:*** Flutrim; ***Spain:*** Flusporan; Funcenal; Micetal.

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)

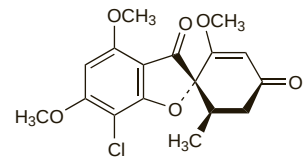
Jpn: Prodif.

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.