Griseofulvin may impair the ability to drive or operate machinery, and has been reported to enhance the effects of alcohol.

Porphyria. Griseofulvin has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

Phenobarbital has been reported to decrease the gastrointestinal absorption of griseofulvin. Plasma concentrations of griseofulvin have also been reported to be reduced by drugs that induce metabolising enzymes.

Griseofulvin may increase the rate of metabolism and diminish the effects of some drugs such as coumarin anticoagulants and oral contraceptives.

Griseofulvin may enhance the effects of alcohol.

Alcohol. In addition to reports of griseofulvin enhancing the effects of alcohol, a severe disulfiram-like reaction to alcohol has been reported in a patient taking griseofulvin.[1]

1. Fett DL, Vukov LF. An unusual case of severe griseofulvin-alcohol interaction. *Ann Emerg Med* 1994; **24:** 95–7.

Bromocriptine. For a report that griseofulvin can block the response to bromocriptine, see p.800.

Salicylates. Griseofulvin has been reported to reduce plasma concentrations of salicylate in a patient taking aspirin, see p.23.

Antimicrobial Action

Griseofulvin is a fungistatic antibiotic that inhibits fungal cell division by disruption of the mitotic spindle structure. It may also interfere with DNA production. It is active against the common dermatophytes, including some species of *Epidermophyton*, *Microsporum*, or *Trichophyton*.

Pharmacokinetics

Absorption of griseofulvin from the gastrointestinal tract is variable and incomplete, but is enhanced by reducing the particle size or when given with a fatty meal. Peak plasma concentrations are reached within 4 hours and are maintained for 10 to 20 hours.

Griseofulvin is about 84% bound to plasma proteins. It is deposited in keratin precursor cells and is concentrated in the stratum corneum of the skin and in the nails and hair, thus preventing fungal invasion of newly formed cells. Concentrations of 12 to 25 micrograms/g are maintained in skin during long-term use, while plasma concentrations remain at about 1 to 2 micrograms/mL. Griseofulvin has an elimination half-life of 9 to 24 hours, and is metabolised by the liver mainly to 6-demethylgriseofulvin and its glucuronide conjugate which are excreted in the urine. A large amount of a dose of griseofulvin of reduced particle size appears unchanged in the faeces; less than 1% is excreted unchanged in the urine; some is excreted in the sweat.

Uses and Administration

Griseofulvin is an antifungal used orally in the treatment of dermatophyte infections. It is generally given when such infections involve the scalp, hair, nails, and skin and do not respond to topical treatment (see Skin Infections, p.521); infections of the soles of the feet, the palms of the hands, and the nails respond slowly.

The usual dose of griseofulvin has been 0.5 to 1 g daily in single or divided doses; children have been given 10 mg/kg daily. These doses are for preparations of griseofulvin of reduced particle size, sometimes known as microcrystalline or microsize griseofulvin. Doses have been reduced by about one-quarter when preparations, available in some countries, containing ultramicrocrystalline or ultramicrosize griseofulvin are used. Griseofulvin should be given with or after meals.

The duration of treatment depends on the thickness of the keratin layer: 2 to 8 weeks for infections of the hair and skin, up to 6 months for infections of the fingernails, and 12 months or more for infections of the toenails.

Griseofulvin is also used as a 1% topical spray in tinea pedis.

◊ Reviews.

1. Fleece D, *et al*. Griseofulvin versus terbinafine in the treatment of tinea capitis: a meta-analysis of randomized, clinical trials. *Pediatrics* 2004; **114:** 1312–15.
2. Gupta AK, *et al*. Meta-analysis: griseofulvin efficacy in the treatment of tinea capitis. *J Drugs Dermatol* 2008; **7:** 369–72.

Non-infective skin disorders. Lichen planus is usually treated with corticosteroids or retinoids (see p.1580) but griseofulvin has been suggested as an alternative to topical corticosteroids in erosive disease.[1] However, some researchers have found it to be of no value.[2]

Dramatic responses of pigmented purpuric dermatoses to griseofulvin 500 to 750 mg daily have been reported in 5 patients.[3]

1. Lamey P-J, Lewis MAO. Oral medicine in practice: white patches. *Br Dent J* 1990; **168:** 147–52.
2. Bagan JV, *et al*. Treatment of lichen planus with griseofulvin. *Oral Surg Oral Med Oral Pathol* 1985; **60:** 608–10.
3. Tamaki K, *et al*. Successful treatment of pigmented purpuric dermatosis with griseofulvin. *Br J Dermatol* 1995; **132:** 159–60.

Preparations

BP 2008: Griseofulvin Tablets;
USP 31: Griseofulvin Capsules; Griseofulvin Oral Suspension; Griseofulvin Tablets; Ultramicrosize Griseofulvin Tablets.

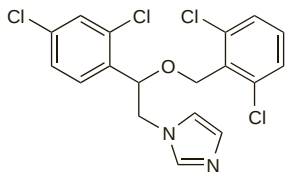
Proprietary Preparations (details are given in Part 3)
Arg.: Grisovin; ***Austral.:*** Griseostatin†; Grisovin; ***Austria:*** Griseomed†; Grisovin; ***Braz.:*** Fulcin; Sporostatin; ***Canad.:*** Fulvicin†; ***Chile:*** Fulvistatin P/G†; ***Fr.:*** Grisefuline; ***Ger.:*** Fulcin S†; Gricin; Griseo; Likuden M; ***India:*** Grisactin; Walavin; ***Indon.:*** Fulcin; Fungistop; Griseofort; Mycostop; ***Irl.:*** Fulcin†; ***Israel:*** Grifulin; ***Ital.:*** Fulcin; Grisovina FP; ***Malaysia:*** Grisuvin; Grivin; Krisovin; Medofulvin†; Myconil†; ***Mex.:*** Fulcin; Fulsivin; Fulvina†; Grisovin; ***Philipp.:*** Grisovin; ***Port.:*** Fulcin†; Grisomicon†; Grisovin; ***S.Afr.:*** Microcidal; ***Singapore:*** Grivin†; Krisovin; Medofulvin†; ***Spain:*** Fulcin; Greosin†; ***Switz.:*** Grisol†; ***Thai.:*** Aofen; Grifulvin; Grisflavin; Grivin; Neofulvin; Trivanex; ***Turk.:*** Gefulvin; Grisovin; ***UK:*** Grisol; Grisovin†; ***USA:*** Gris-PEG; ***Venez.:*** Fulvin†; Grisovin.

Multi-ingredient: ***Arg.:*** Griseoplus.

Isoconazole *(BAN, USAN, rINN)*

Isoconazol; Isoconazolum; Isokonatsoli; Isokonazol; Izokonazol; Izokonazolas. 1-[2,4-Dichloro-β-(2,6-dichlorobenzyloxy)phenethyl]imidazole.

Изоконазол
$C_{18}H_{14}Cl_4N_2O$ = 416.1.
CAS — 27523-40-6.
ATC — D01AC05; G01AF07.
ATC Vet — QD01AC05; QG01AF07.



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

Isoconazole Nitrate *(BANM, rINNM)*

Isoconazole, bitrate d'; Isoconazole, Nitrate d'; Isoconazoli nitras; Isokonatsolinitraatti; Isokonazolnitrat; Isokonazol-nitrát; Izokonazol Nitrat; Izokonazol-nitrát; Izokonazolo nitratas; Nitrato de isoconazol; R-15454.

Изоконазола Нитрат
$C_{18}H_{14}Cl_4N_2O,HNO_3$ = 479.1.
CAS — 24168-96-5 (isoconazole mononitrate); 40036-10-0 (isoconazole nitrate).
ATC — D01AC05; G01AF07.
ATC Vet — QD01AC05; QG01AF07.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Isoconazole Nitrate). A white or almost white powder. Very slightly soluble in water; slightly soluble in alcohol; soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

Local reactions including burning or itching may occur after application of isoconazole.

Intravaginal preparations of azole antifungals may damage latex contraceptives and additional contraceptive measures are therefore necessary during local application.

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

Antimicrobial Action

Isoconazole is an imidazole antifungal active against a wide spectrum of fungi including *Candida* spp., dermatophytes, and *Malassezia furfur*. It is also active against some Gram-positive bacteria.

Uses and Administration

Isoconazole is an imidazole antifungal used locally as the nitrate in the treatment of vaginal mycoses, particularly due to *Candida* spp. (p.518) and in fungal skin infections (p.521). For vaginal infections it is usually given as pessaries in a single dose of 600 mg or 300 mg daily for 3 days, or as a 1% vaginal cream daily for 7 days. For skin infections a 1% or 2% cream or other topical formulation has been used.

Preparations

BP 2008: Isoconazole Pessaries.

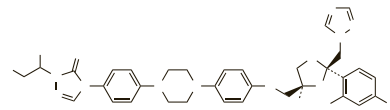
Proprietary Preparations (details are given in Part 3)
Arg.: Isomicot; Mupaten; ***Austria:*** Gyno-Travogen; Travogen; ***Belg.:*** Travogen; ***Braz.:*** Gino Monipax†; Gino-Isomax; Ginotrax; Gyno Icaden; Gyno-Mycel†; Gynoplus†; Icaden; Isomax; Micaden; Mycel Gyno; Neo Isocaden; ***Chile:*** Ufarin; ***Fr.:*** Fazol; Fazol G; ***Ger.:*** Travogen†; ***Gr.:*** Travogen; ***Hong Kong:*** Gyno-Travogen†; Travogen; ***Israel:*** Isogen; ***Ital.:*** Isogyn; Travogen; ***Malaysia:*** Travogen; ***Mex.:*** Icaden; Nocazin; ***Philipp.:*** Travogen; ***Pol.:*** Gyno-Travogen; Travogen; ***Port.:*** Gino-Travogen; ***Rus.:*** Gyno-Travogen (Гино-травоген); Travogen (Травоген); ***Singapore:*** Gyno-Travogen; Travogen; ***Switz.:*** Gyno-Travogen; Travogen; ***Thai.:*** Nacozil†; Travogen; ***Turk.:*** Gyno-Travogen; Travogen; ***Venez.:*** Icaden; Noginox.

Multi-ingredient: ***Arg.:*** Scheriderm; ***Austria:*** Travocort; ***Belg.:*** Travocort; ***Ger.:*** Bi-Vaspit†; Travocort; ***Gr.:*** Travocort; ***Hong Kong:*** Travocort; ***Indon.:*** Travocort; ***Irl.:*** Travocort; ***Israel:*** Isocort; Tevaderm; ***Ital.:*** Travocort; ***Malaysia:*** Isoradin; Travocort; ***Mex.:*** Scheriderm; ***Philipp.:*** Travocort; ***Pol.:*** Travocort; ***Port.:*** Travocort; ***Rus.:*** Travocort (Травокорт); ***S.Afr.:*** Travocort; ***Singapore:*** Travocort; ***Switz.:*** Travocort; ***Thai.:*** Travocort; ***Turk.:*** Travazol; Travocort.

Itraconazole *(BAN, USAN, rINN)*

Itraconazol; Itraconazolum; Itrakonatsoli; Itrakonazol; Itrakonazolas; Oriconazole; R-51211. (±)-2-*sec*-Butyl-4-[4-(4-{4-[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethoxy]phenyl}-piperazin-1-yl)phenyl]-2,4-dihydro-1,2,4-triazol-3-one.

Итраконазол
$C_{35}H_{38}Cl_2N_8O_4$ = 705.6.
CAS — 84625-61-6.
ATC — J02AC02.
ATC Vet — QJ02AC02.



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

Adverse Effects

The most common adverse effects associated with itraconazole include dyspepsia, abdominal pain, nausea, vomiting, constipation, diarrhoea, headache, and dizziness. Others include allergic reactions such as pruritus, rash, urticaria, and angioedema. Isolated cases of the Stevens-Johnson syndrome have been associated with itraconazole.

An increase in liver enzyme values has occurred in some patients and cases of hepatitis and cholestatic jaundice have been observed, especially in those treated for more than one month. There have been rare cases of liver failure and death.

Heart failure and pulmonary oedema have been reported rarely and serious cardiovascular events including arrhythmias and sudden death have been attributed to drug interactions in patients receiving itraconazole (see Interactions, below).

Alopecia, oedema, and hypokalaemia have also been associated with prolonged use. Menstrual disorders and peripheral neuropathy have been reported in a few patients.

Incidence of adverse effects. Itraconazole 50 to 400 mg daily for a median of 5 months was considered to be well tolerated in 189 patients with systemic fungal infections.[1] Of 86 patients with

underlying disease, including 49 with AIDS, 16 with diabetes, and 23 with malignancy, nausea and vomiting occurred in 19 patients, hypertriglyceridaemia in 16, hypokalaemia in 11, and elevated liver enzyme values in 13. The role of itraconazole in hypertriglyceridaemia could not be assessed because all the samples were not drawn in the fasting state and hypertriglyceridaemia is a complication of HIV infection. Gynaecomastia occurred in 2 patients, 1 of whom also took spironolactone. Rash occurred in 4 patients.

Of 49 patients taking itraconazole 100 to 400 mg daily for up to 39 months, 23 did not experience adverse effects during treatment,[2] while 6 had nausea and vomiting, 5 developed oedema, and 2 developed hypertension; 3 of the patients who developed oedema and 1 who became hypertensive were diabetic. Three patients stopped itraconazole, 1 due to vomiting, 1 to leucopenia, and 1 to nephrotic syndrome. The patient with nephrotic syndrome had pre-existing oedema and hypertension; the syndrome cleared when itraconazole was stopped.

1. Tucker RM, *et al.* Adverse events associated with itraconazole in 189 patients on chronic therapy. *J Antimicrob Chemother* 1990; **26:** 561–6.
2. Graybill JR, *et al.* Itraconazole treatment of coccidioidomycosis. *Am J Med* 1990; **89:** 282–90.

Effects on the heart. Between September 1992, when itraconazole was approved in the USA, and April 2001, the FDA had received 58 reports of potential cases of heart failure associated with itraconazole.[1] There had been 28 patients admitted to hospital, and 13 had died. However, a causal relationship was difficult to prove. Overall, 43 patients had risk factors or diseases which might confound an association between the use of itraconazole and development of heart failure. Unpublished studies in *dogs* and humans had suggested a negative inotropic effect with intravenous itraconazole.

In August 2001, the UK CSM published a similar alert.[2] By this time, about 67 million patients worldwide had received itraconazole and there had been 75 spontaneously reported cases of suspected heart failure and an additional 63 reports of oedema suggestive of heart failure associated with oral formulations; there had been only 1 report of suspected heart failure in the UK. The CSM considered that the risk of heart failure with itraconazole was low, especially in young healthy patients receiving short courses of treatment (e.g. for vulvovaginal candidiasis). However, the risks appeared to be higher for older patients, patients with pre-existing heart disease or risk factors for heart failure, and for those receiving high doses and longer treatment courses (e.g. for onychomycosis).

The CSM[2] therefore advised caution when prescribing itraconazole to patients at risk of heart failure, whereas the FDA[1] contraindicated it for the treatment of onychomycosis in patients with evidence of ventricular dysfunction.

1. Ahmad SR, *et al.* Congestive heart failure associated with itraconazole. *Lancet* 2001; **357:** 1766–7.
2. Committee on Safety of Medicines. Cardiodepressant effect of itraconazole (Sporanox). *Current Problems* 2001; **27:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 04/06/06)

Precautions

Itraconazole has caused abnormalities in fetal development in *rodents* and is therefore contra-indicated in pregnancy. For further information, see Pregnancy, under Precautions of Fluconazole, p.532.

Itraconazole should be avoided in patients with hepatic impairment. Liver function should be monitored if treatment lasts more than one month or if there are symptoms suggestive of hepatitis. Treatment should be stopped if abnormal liver function is detected. Plasma-itraconazole concentrations should be monitored in patients with active liver disease and the dosage adjusted if necessary.

Dose adjustments may also be required in some patients with renal impairment. Licensed product information warns that the use of intravenous preparations of itraconazole formulated with hydroxypropylbetadex is contra-indicated in patients with a creatinine clearance of less than 30 mL/minute.

Itraconazole should be stopped if neuropathy develops.

Itraconazole should not be used for the treatment of less severe fungal infections such as onychomycosis in patients with evidence of, or a history of, ventricular dysfunction such as heart failure.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of itraconazole. In this case absorption may be improved by giving itraconazole with an acidic drink, such as a cola beverage.

Breast feeding. Breast feeding while receiving itraconazole is not recommended by the manufacturer although only small amounts of itraconazole are distributed into breast milk.

Interactions

Enzyme-inducing drugs such as carbamazepine, isoniazid, nevirapine, phenobarbital, phenytoin, rifabutin, or rifampicin may *decrease* plasma concentrations of itraconazole sufficiently to reduce its effectiveness. Conversely, enzyme inhibitors such as clarithromycin, erythromycin, HIV-protease inhibitors, including ritonavir-boosted HIV-protease inhibitors, may *increase* plasma concentrations of itraconazole. Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, proton pump inhibitors, and histamine H_2-receptor antagonists, may reduce the absorption of itraconazole. Like other triazole antifungals, itraconazole is a potent inhibitor of the cytochrome P450 isoenzyme CYP3A4, and may increase plasma concentrations of other drugs reliant upon it for their metabolism. This increases the risk of adverse effects and such combinations should be given with caution and careful monitoring, if at all. Drugs so affected may include:

- *antiarrhythmics* such as dofetilide and quinidine
- *antiepileptics* such as carbamazepine (which in turn decreases the concentration of the antifungal, see above)
- *antihistamines* such as astemizole and terfenadine
- the *antimycobacterial* rifabutin (which again also decreases antifungal concentrations)
- *antineoplastics* such as busulfan, docetaxel, and the vinca alkaloids
- *antipsychotics* such as pimozide and sertindole
- *anxiolytics and sedatives* such as buspirone
- *benzodiazepines* such as alprazolam, diazepam, midazolam, and triazolam
- *calcium channel blockers* such as verapamil, and the dihydropyridines felodipine, nifedipine, and nisoldipine (see also below)
- *cardiac glycosides* such as digoxin
- some *corticosteroids* such as budesonide, dexamethasone, fluticasone and methylprednisolone
- the *coumarin anticoagulant* warfarin
- *ergot alkaloids* such as dihydroergotamine, ergometrine, ergotamine, and methylergometrine
- the *gastrointestinal prokinetic* cisapride
- *HIV-protease inhibitors* such as indinavir, ritonavir, and saquinavir (concentrations of the antifungal may be increased in turn by indinavir, ritonavir, or co-formulated lopinavir-ritonavir, but not by saquinavir)
- *immunosuppressants* such as ciclosporin, sirolimus, and tacrolimus
- *opioids* such as alfentanil and levacetylmethadol
- some *oral hypoglycaemics*
- the *phosphodiesterase inhibitors* sildenafil and vardenafil
- *statins* (HMG Co-A reductase inhibitors) such as atorvastatin, lovastatin, and simvastatin

Where drugs metabolised via CYP3A4 also prolong the QT interval, the risk of serious cardiovascular effects such as torsade de pointes means that the combination should be avoided; this includes astemizole, cisapride, dofetilide, levacetylmethadol, pimozide, quinidine, sertindole, and terfenadine. Care is also required with calcium channel blockers, which may increase the risk of congestive heart failure if given together, and nisoldipine in particular is considered contra-indicated. Use with the statins is also best avoided because of the risk of muscle damage.

◊ Reviews of drug interactions with azole antifungals.

1. Baciewicz AM, Baciewicz FA. Ketoconazole and fluconazole drug interactions. *Arch Intern Med* 1993; **153:** 1970–6.
2. Lomaestro BM, Piatek MA. Update on drug interactions with azole antifungal agents. *Ann Pharmacother* 1998; **32:** 915–28.
3. Venkatakrishnan K, *et al.* Effects of the antifungal agents on oxidative drug metabolism: clinical relevance. *Clin Pharmacokinet* 2000; **38:** 111–80.

Immunosuppressants. Fatal hepatitis occurred in a 68-year-old woman[1] after 2 months of use of itraconazole and *leflunomide*. The authors suggested that the combined hepatotoxicity of both drugs might have accounted for this.

1. Legras A, *et al.* Fatal hepatitis with leflunomide and itraconazole. *Am J Med* 2002; **113:** 352–3.

Metal ions. Didanosine in a formulation containing aluminium and magnesium ion buffering agents could reduce the absorption of itraconazole due to the resultant increase in gastric pH.[1]

1. Moreno F, *et al.* Itraconazole-didanosine excipient interaction. *JAMA* 1993; **269:** 1508.

Antimicrobial Action

Itraconazole is a triazole antifungal drug that in sensitive fungi inhibits cytochrome P450-dependent enzymes resulting in impairment of ergosterol synthesis in fungal cell membranes. It has a slightly wider spectrum of activity than ketoconazole. It is active against *Aspergillus* spp., *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Epidermophyton* spp., *Histoplasma capsulatum*, *Malassezia furfur*, *Microsporum* spp., *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, and *Trichophyton* spp. Itraconazole also has some antiprotozoal activity against *Leishmania* spp.

Acquired resistance to itraconazole is rare but ketoconazole-resistant strains of *Candida albicans* have been found to be cross resistant to itraconazole.

Microbiological interactions. Synergistic antifungal effects were seen *in vitro* with terbinafine and itraconazole against strains of *Candida albicans*[1] and *Scedosporium prolificans*.[2] For effects on the antifungal activity of azoles 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.
2. Meletiadis J, *et al.* In vitro interaction of terbinafine with itraconazole against clinical isolates of Scedosporium prolificans. *Antimicrob Agents Chemother* 2000; **44:** 470–2.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles, see under Antimicrobial Action of Fluconazole, p.533. Decreased susceptibility to itraconazole and cross-resistance to fluconazole has been reported in *C. albicans* isolated from patients with AIDS given long-term prophylaxis with itraconazole.[1] *Aspergillus fumigatus* resistant to itraconazole has also been seen.[2,3]

1. 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.
2. Denning DW, *et al.* Itraconazole resistance in Aspergillus fumigatus. *Antimicrob Agents Chemother* 1997; **41:** 1364–8.
3. Dannaoui E, *et al.* Acquired itraconazole resistance in Aspergillus fumigatus. *J Antimicrob Chemother* 2001; **47:** 333–340.

Pharmacokinetics

Itraconazole is absorbed from the gastrointestinal tract when given orally either as capsules containing itraconazole coated onto sugar spheres or as an oral liquid formulated with hydroxypropylbetadex. Absorption from the capsule formulation is enhanced by an acidic gastric environment and is greatest when doses are taken with food; absorption from the oral liquid is not dependent on an acid environment, and absorption is greatest in the fasting state. Peak plasma concentrations are achieved between 1.5 and 5 hours after a dose of either formulation, and steady state is reached within 15 days during daily dosing. Peak plasma concentrations at steady state of about 2 micrograms/mL have been reported after daily doses of 200 mg.

Bioavailability increases with doses of 100 to 400 mg in such a manner as to suggest that itraconazole undergoes saturable metabolism. Itraconazole is highly protein bound; only 0.2% circulates as free drug. Itraconazole is widely distributed but only small amounts diffuse into the CSF. Concentrations attained in the skin, sebum, pus, and many organs and tissues are several times higher than simultaneous plasma concentrations. Therapeutic concentrations of itraconazole remain in the skin and mucous membranes for 1 to 4 weeks after the drug is stopped. Small amounts are distributed into breast milk.

Itraconazole is metabolised in the liver mainly by cytochrome P450 isoenzyme CYP3A4. The major metabolite, hydroxyitraconazole, has antifungal activity

comparable with that of itraconazole. Itraconazole is also excreted as inactive metabolites in the bile or urine; 3 to 18% is excreted in the faeces as unchanged drug. Small amounts are eliminated in the stratum corneum and hair. Itraconazole is not removed by dialysis.

The elimination half-life following a single 100-mg dose has been reported as 20 hours, increasing to 30 to 40 hours with continued use.

Uses and Administration

Itraconazole is a triazole antifungal given orally for the treatment of oropharyngeal and vulvovaginal candidiasis, for pityriasis versicolor, for dermatophytoses unresponsive to topical treatment, for onychomycosis, and for systemic infections including aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis. It is also given for the prophylaxis of fungal infections in immunocompromised patients. The place of itraconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p.517.

Doses of itraconazole oral liquid and capsules are not equivalent and may not be used interchangeably.

In the UK, itraconazole **oral liquid** is licensed for use in oral and oesophageal candidiasis in a dose of 200 mg daily for 1 week; it may be taken as a single daily dose, or, preferably, in 2 divided doses, the liquid being retained in the mouth for 20 seconds before swallowing. If there is no response after a week, treatment may be continued for a further week. In the USA, a similar regimen is licensed for oropharyngeal candidiasis, but in oesophageal candidiasis an alternative regimen of 100 mg daily for at least 3 weeks is preferred, although the dose may be increased to 200 mg daily if necessary.

For patients with fluconazole-resistant infections the dose in the UK is 100 to 200 mg twice daily for 2 weeks; if there is no response, 100 mg twice daily may be given for a further 2 weeks. In the USA the recommended dose is 100 mg twice daily.

Itraconazole oral liquid is also licensed in the UK for prophylaxis of susceptible fungal infections in immunocompromised patients, in doses of 5 mg/kg daily, in 2 divided doses.

The following oral doses all apply to itraconazole **capsules**. The dose in oropharyngeal candidiasis is 100 mg (or 200 mg in patients with AIDS or neutropenia) daily for 15 days. Vulvovaginal candidiasis may be treated with itraconazole 200 mg twice daily for 1 day. Pityriasis versicolor may be treated with itraconazole 200 mg daily for 7 days. For dermatophytoses the dose is 100 mg daily for 15 days or 200 mg daily for 7 days in tinea corporis or tinea cruris; doses are 100 mg daily for 30 days or 200 mg twice daily for 7 days in tinea pedis or tinea manuum. For nail infections the dose is 200 mg daily for 3 months or pulse therapy with 200 mg twice daily for 7 days repeated once (for fingernails) or twice (for toenails) after drug-free intervals of 21 days.

For systemic infections, itraconazole capsules are given in usual doses of 100 to 200 mg once daily, increased to 200 mg twice daily for invasive or disseminated infections, including cryptococcal meningitis. In life-threatening infections a loading dose of 200 mg three times daily for 3 days has been given. A dose of 200 mg daily is used for primary or secondary prophylaxis in neutropenic patients or those with AIDS. Absorption may be impaired in these patients and monitoring of plasma concentrations is advised with an increase in dose to 200 mg twice daily if necessary. This higher dose is recommended routinely by some authorities in the USA such as the *Centers for Disease Control and Prevention*.

Itraconazole may also be given by **intravenous infusion** in a dose of 200 mg given twice daily over 1 hour for two days, then 200 mg daily thereafter.

◊ Reviews.

1. Haria M, *et al.* Itraconazole: a reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections. *Drugs* 1996; **51:** 585–620.
2. Pierard GE, *et al.* Itraconazole. *Expert Opin Pharmacother* 2000; **1:** 287–304.
3. Stevens DA (ed). Managing fungal infections in the 21st century: focus on itraconazole. *Drugs* 2001; **61** (suppl 1): 1–56.
4. Slain D, *et al.* Intravenous itraconazole. *Ann Pharmacother* 2001; **35:** 720–9.
5. Boogaerts M, Maertens J. Clinical experience with itraconazole in systemic fungal infections. *Drugs* 2001; **61** (suppl 1): 39–47.
6. Maertens J, Boogaerts M. The place for itraconazole in treatment. *J Antimicrob Chemother* 2005; **56** (suppl 1): i33–i38.
7. Potter M. Strategies for managing systemic fungal infection and the place of itraconazole. *J Antimicrob Chemother* 2005; **56** (suppl 1): i49–i54.

Administration. ***HIGH DOSES***. Doses of itraconazole 600 mg daily in two divided doses for 3 to 16 months were used in 8 patients with systemic mycoses resistant to conventional therapy.[1] Two patients with AIDS and cryptococcal meningitis failed to respond and 2 who responded initially later relapsed or developed progressive disease when the dose was reduced. The main adverse effects were hypokalaemia, hypertension, and oedema possibly associated with adrenal suppression.

In a patient with cerebral aspergillosis, itraconazole 800 mg daily for 5 months then 400 mg daily for a further 4½ months produced complete resolution of cerebral lesions.[2]

1. Sharkey PK, *et al.* High-dose itraconazole in the treatment of severe mycoses. *Antimicrob Agents Chemother* 1991; **35:** 707–13.
2. Sánchez C, *et al.* Treatment of cerebral aspergillosis with itraconazole: do high doses improve the prognosis? *Clin Infect Dis* 1995; **21:** 1485–7.

Administration in children and neonates. Itraconazole has been used in children in the treatment of tinea capitis.[1] Doses were 50 mg daily by mouth for those below 20 kg and 100 mg daily for those weighing 20 kg or more.

A review of the use of itraconazole in children[2] considered oral itraconazole to be safe and effective against most fungal organisms causing superficial infections.

Itraconazole was given to 2 premature infants with disseminated candidiasis in a dose of 10 mg/kg daily in two divided doses for 3 or 4 weeks without adverse effects.[3] Treatment was successful in both infants.

Although itraconazole oral liquid is not licensed for use in children in the UK, and the capsules are only licensed from 12 years of age, the *BNFC* suggests the following daily ***oral*** doses, given as a single dose (unless otherwise specified):

for **oropharyngeal candidiasis**:

- 1 month to 12 years of age, 3 to 5 mg/kg (to a maximum of 100 mg) daily for 15 days; up to 200 mg daily may be given to patients with neutropenia or AIDS
- 12 to 18 years of age, 100 mg (200 mg in those with neutropenia or AIDS) daily for 15 days

for **dermatophyte infections**:

- 1 month to 12 years of age, 3 to 5 mg/kg daily; this is given to a maximum of 200 mg daily for 7 days (pityriasis versicolor), to a maximum of 100 mg daily for 15 days (tinea corporis and tinea cruris), or to a maximum of 100 mg daily for 30 days (tinea pedis and tinea manuum)
- 12 to 18 years of age, 200 mg daily for 7 days (pityriasis versicolor); 100 mg daily for 15 days or as in pityriasis (tinea corporis and tinea cruris); or 100 mg daily for 30 days or 200 mg *twice* daily for 7 days (tinea pedis and tinea manuum)

for **onychomycosis**, from 1 year of age:

- 1 to 12 years, courses of 5 mg/kg daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections
- 12 to 18 years, either 200 mg daily for 3 months, or courses of 200 mg *twice* daily for 7 days, repeated after intervals of 21 days to a total of 2 courses for infections of the fingernails and 3 courses for toenail infections

for **histoplasmosis** or for **systemic fungal infections** such as aspergillosis, candidiasis, and cryptococcosis (including cryptococcal meningitis) where other antifungal drugs are inappropriate or ineffective:

- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) once or twice daily; the *twice* daily dose should be used in invasive or disseminated disease or cryptococcal meningitis. For intravenous doses see below

for **maintenance in AIDS patients** to prevent relapse of underlying fungal infection, or for **prophylaxis in neutropenia** when standard therapy is inappropriate:

- from 1 month of age to 18 years, 5 mg/kg (to a maximum of 200 mg) daily, increased to *twice* daily if plasma-itraconazole concentrations are low

for **prophylaxis in haematological malignancy or bone-marrow transplantation** (in patients expected to become neutropenic), where standard therapy is inappropriate the *oral liquid* may be given as follows:

- from 1 month of age to 18 years, 2.5 mg/kg *twice* daily, starting before transplantation or chemotherapy and continued until the neutrophil count recovers

Like the oral liquid the intravenous product is not licensed in children in the UK; the *BNFC* suggests the following ***intravenous*** doses by infusion in children with **systemic fungal infections**:

- from 1 month of age to 18 years, 2.5 mg/kg (to a maximum of 200 mg) every 12 hours for 2 days, then the same dose once daily for a maximum of 12 days. Doses should be given by diluting 250 mg as the intravenous concentrate in 50 mL of sodium chloride 0.9% and infusing over 60 minutes

1. Möhrenschlager M, *et al*. Optimizing the therapeutic approach in tinea capitis of childhood with itraconazole. *Br J Dermatol* 2000; **143:** 1011–15.
2. Gupta AK, *et al.* Efficacy and safety of itraconazole use in children. *Dermatol Clin* 2003; **21:** 521–35.
3. Bhandari V, Narang A. Oral itraconazole therapy for disseminated candidiasis in low birth weight infants. *J Pediatr* 1992; **120:** 330.

Amoebic infections. Itraconazole has been suggested for *Acanthamoeba* keratitis (p.822), when it is given orally with topical miconazole.

Leishmaniasis. When systemic therapy is required for the treatment of leishmaniasis (p.824), pentavalent antimonials are most commonly used. The successful use of itraconazole has been reported in a few patients[1-4] with cutaneous disease but infections with *Leishmania aethiopica* may not respond.[5] Although a pilot study[6] in patients with mucocutaneous leishmaniasis reported benefit with itraconazole this was not confirmed in another study[7] where the response was only transient in the majority of patients. Similarly, itraconazole with terbinafine has been found to be ineffective in post kala-azar dermal leishmaniasis.[8]

1. Albanese G, *et al.* Cutaneous leishmaniasis: treatment with itraconazole. *Arch Dermatol* 1989; **125:** 1540–2.
2. Pialoux G, *et al.* Cutaneous leishmaniasis in an AIDS patient: cure with itraconazole. *J Infect Dis* 1990; **162:** 1221–2.
3. Dogra J, Saxena VN. Itraconazole and leishmaniasis: a randomised double-blind trial in cutaneous disease. *Int J Parasitol* 1996; **26:** 1413–15.
4. Consigli J, *et al.* Cutaneous leishmaniasis: successful treatment with itraconazole. *Int J Dermatol* 2006; **45:** 46–9.
5. Akuffo H, *et al.* The use of itraconazole in the treatment of leishmaniasis caused by Leishmania aethiopica. *Trans R Soc Trop Med Hyg* 1990; **84:** 532–4.
6. Amato VS, *et al.* Use of itraconazole in the treatment of mucocutaneous leishmaniasis: a pilot study. *Int J Infect Dis* 2000; **4:** 153–7.
7. Calvopina M, *et al.* Itraconazole in the treatment of New World mucocutaneous leishmaniasis. *Int J Dermatol* 2004; **43:** 659–63.
8. Khalil EAG, *et al.* Failure of a combination of two antifungal drugs, terbinafine plus itraconazole, in Sudanese post kala-azar dermal leishmaniasis. *Trans R Soc Trop Med Hyg* 1996; **90:** 187–8.

Trypanosomiasis. Itraconazole, alone or with allopurinol, may produce beneficial responses in American trypanosomiasis (p.827).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: ITC†; Itrac; Micotenk; Nitridazol; Panastat; Salimidin; Sporanox; ***Austral.:*** Sporanox; ***Austria:*** Itrabene; Sporanox; ***Belg.:*** Sporanox; ***Braz.:*** Estiranox; Fungonax; Itracotan; Itrahexal†; Itranax†; Itraspor; Itrazol; Neo Itrax; Sporanox; Spozol; Tracnox†; Traconal; Traconax†; Tracozon; Tranazol†; Tratzol; Traxonol†; ***Canad.:*** Sporanox; ***Chile:*** Itodal; Sporanox; Teramic; ***Cz.:*** Cladostad; Prokanazol; Sporanox; ***Denm.:*** Niddazol; Sporanox; ***Fin.:*** Sporanox; ***Fr.:*** Sporanox; ***Ger.:*** Canifug Itra; Itracol; Sempera; Siros; ***Gr.:*** Assosept-S; Bevonazole; Brovicton; Deratil; Etrel; Flunol; Idranox; Isoflon; Itrabest; Itracon; Itraconal; Itralfa; Itraviron; Itrazol; Laverio; Lorenzol; Mesmor; Micronazol; Prominox; Soprazon; Sporanox; Sporizole; Stas; Sterginox; Zetilox; ***Hong Kong:*** Aranox; Quali-itrazole; Sporanox; ***Hung.:*** Cladostad; Omicral; Orungal; ***India:*** Candistat; Canditral; Itracan; ***Indon.:*** Forcanox; Fungitrazol; Furolnok; Itzol; Nufatrac; Sporacid; Sporanox; Spyrocon; Trachon; Unitrac; Zitrazol; ***Irl.:*** Sporanox; ***Israel:*** Itranol; Sporanox; ***Ital.:*** Sporanox; Trazer; Triasporin; ***Jpn:*** Itrizole; ***Malaysia:*** Canditral; Inox; Sporanox; Unitrac; ***Mex.:*** Carexan; Conamed; Congox; Derusil; Ergospharma; Fitocyd; Fulzoltec†; Fuzoltec; Imazol; Iqcona; Isoporum; Isox; Itranax; Lozartil; Rixtal; Seritral; Silicsan; Sinozol; Solmavin; Sporanox; Steitraz; Trax; Z-Fin; Zolken; ***Neth.:*** Trisporal; ***Norw.:*** Sporanox; ***NZ:*** Sporanox; ***Philipp.:*** Sporanox; ***Pol.:*** Orungal; Trioxal; ***Port.:*** Sporanox; ***Rus.:*** Irunine (Ируниh); Orungal (Оруngал); Orungamin (Оруngамин); Orunit (Оруnит); Rumycoz (Румикоз); ***S.Afr.:*** Adco-Sporozole; Sporanox; ***Singapore:*** Canditral†; Sporanox; ***Spain:*** Canadiol; Hongoseril; Oromic; Sporanox; ***Swed.:*** Sporanox; ***Switz.:*** Sporanox; ***Thai.:*** Canditral; Icona; Itra; Itracon; Norspor; Spazol; Sporal; Sporlab; Spornar; ***Turk.:*** Funit; Itraspor; Sporex; ***UK:*** Sporanox; ***USA:*** Sporanox; ***Venez.:*** Fungosin; Sporanox.

Multi-ingredient: ***Mex.:*** Sepia; Sporasec; ***Venez.:*** Sporasec.

Ketoconazole *(BAN, USAN, rINN)*

Ketoconazol; Kétoconazole; Ketoconazolum; Ketokonatsoli; Ketokonazol; Ketokonazolas; R-41400. (±)-*cis*-1-Acetyl-4-{4-[2-(2,4-dichlorophenyl)-2-imidazol-1-ylmethyl-1,3-dioxolan-4-ylmethoxy]phenyl}piperazine.

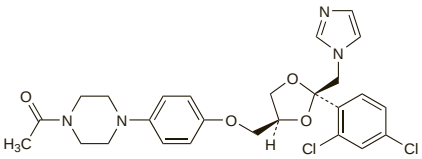
Кетоконазол

$C_{26}H_{28}Cl_2N_4O_4$ = 531.4.

CAS — 65277-42-1.

ATC — D01AC08; G01AF11; J02AB02.

ATC Vet — QD01AC08; QG01AF11; QJ02AB02.



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

Ph. Eur. 6.2 (Ketoconazole). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

Adverse Effects

Gastrointestinal disturbances are the most frequently reported adverse effect after the oral use of ketoconazole. Nausea and vomiting have been reported in about 3% of patients, and abdominal pain in about 1%. These adverse effects are dose-related and may be minimised by giving ketoconazole with food. Asymptomatic, transient elevations in serum concentrations of liver enzymes may occur in about 10% of patients. Hepatitis has been reported and the risk appears to increase if treatment with ketoconazole is continued for longer than 2 weeks; it is usually reversible on stopping ketoconazole but fatalities have occurred. Ketoconazole interferes with steroid biosynthesis and adverse endocrine effects include gynaecomastia, oligospermia, menstrual irregularities, and adrenal cortex suppression, especially at high doses.

Other adverse effects include allergic reactions such as urticaria and angioedema, and rare cases of anaphylaxis after the first dose have been reported. Pruritus, rash, alopecia, headache, dizziness, impotence, and somnolence may also occur. Thrombocytopenia, paraesthesia, raised intracranial pressure, and photophobia have been reported rarely.

After topical use of ketoconazole, irritation, dermatitis, or a burning sensation has occurred.

Effects on the blood. A case of fatal aplastic anaemia was reported[1] in a 23-year-old woman who had taken ketoconazole for 4 days for the treatment of vaginal discharge.

1. Duman D, *et al*. Fatal aplastic anemia during treatment with ketoconazole. *Am J Med* 2001; **111:** 737.

Effects on endocrine function. Oral ketoconazole blocks testosterone synthesis and adrenal response to corticotropin, resulting in azospermia and oligospermia, gynaecomastia, impotence and decreased libido, and adrenal insufficiency.[1-8] As an inhibitor of steroid production, ketoconazole is valuable in controlling hypercortisolism and is used therapeutically in some endocrine disorders and prostatic cancer. For further discussion see under Uses and Administration, below.

1. DeFelice R, *et al.* Gynecomastia with ketoconazole. *Antimicrob Agents Chemother* 1981; **19:** 1073–4.
2. Pont A, *et al.* High-dose ketoconazole therapy and adrenal and testicular function in humans. *Arch Intern Med* 1984; **144:** 2150–3.
3. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i:** 44–5.
4. Dandona P, *et al.* Non-suppression of cortisol secretion by long term treatment with ketoconazole in patients with acute leukaemia. *J Clin Pathol* 1985; **38:** 677–8.
5. Pillans PI, *et al.* Hyponatraemia and confusion in a patient taking ketoconazole. *Lancet* 1985; **i:** 821–2.
6. McCance DR, *et al.* Acute hypoadrenalism and hepatotoxicity after treatment with ketoconazole. *Lancet* 1987; **i:** 573.
7. Best TR, *et al.* Persistent adrenal insufficiency secondary to low-dose ketoconazole therapy. *Am J Med* 1987; **82:** 676–80.
8. Khosla S, *et al.* Adrenal crisis in the setting of high-dose ketoconazole therapy. *Arch Intern Med* 1989; **149:** 802–4.

Effects on the liver. Hepatic adverse reactions to oral ketoconazole are well known.[1-4] Transient minor elevations of liver enzymes without clinical signs or symptoms of hepatic disease occur in about 10% of patients and may occur at any stage of treatment. Although this reaction is not usually clinically important it may signal the onset of more serious hepatic injury and indicates the need for close monitoring of liver function. Symptomatic hepatic reactions are much rarer (less than 0.1% of patients) but are potentially fatal. There is usually a hepatocellular pattern of damage and sometimes cholestasis. Patients at increased risk of hepatic injury include those with a history of liver disease, those aged over 50, especially women, and those requiring prolonged treatment. It is important to monitor liver function during treatment as well as to limit the length of treatment. If liver enzyme values continue to rise or jaundice or hepatitis occur, ketoconazole should be withdrawn immediately since fatalities have occurred in patients who continued treatment after signs of hepatic injury developed.

1. Janssen PA, Symoens JE. Hepatic reactions during ketoconazole treatment. *Am J Med* 1983; **74:** 80–5.
2. Lewis JH, *et al*. Hepatic injury associated with ketoconazole therapy. *Gastroenterology* 1984; **86:** 503–13.
3. Lake-Bakaar G, *et al*. Hepatic reactions associated with ketoconazole in the United Kingdom. *BMJ* 1987; **294:** 419–21.
4. García Rodríguez LA, *et al*. A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *Br J Clin Pharmacol* 1999; **48:** 847–52.

Precautions

Since ketoconazole has been reported to cause hepatotoxicity it should not be given to patients with pre-existing liver disease. Patients given ketoconazole should be monitored for symptoms of hepatitis; also, liver function tests should be performed before starting oral treatment with ketoconazole lasting for more than 14 days and then at least monthly throughout therapy.

Ketoconazole has been shown to be teratogenic in *animal* studies and its use is generally not recommended during pregnancy. For a discussion of the caution needed when using azole antifungals during pregnancy, see under Pregnancy in Precautions of Fluconazole, p.532.

Hypochlorhydria, which may be present in patients with AIDS, can reduce absorption of ketoconazole. In this case absorption may be improved by giving ketoconazole with an acidic drink, such as a cola beverage.

Breast feeding. Ketoconazole is excreted in breast milk and licensed product information states that oral use should be avoided during breast feeding. However, no adverse effects were seen in a breast-fed infant whose mother was receiving ketoconazole;[1] it was calculated that the infant was exposed to about 0.4% of the usual therapeutic dose of ketoconazole for this age group. The American Academy of Pediatrics considers[2] that use of ketoconazole is therefore usually compatible with breast feeding.

1. Moretti ME, *et al*. Disposition of maternal ketoconazole in breast milk. *Am J Obstet Gynecol* 1995; **173:** 1625–6.
2. 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 28/06/05)

Porphyria. Ketoconazole is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

Use of drugs that reduce stomach acidity, such as antimuscarinics, antacids, histamine H_2-antagonists, and proton pump inhibitors, may reduce the absorption of ketoconazole. Absorption of ketoconazole may also be reduced by sucralfate. Enzyme-inducing drugs such as rifampicin, isoniazid, efavirenz, nevirapine, or phenytoin may reduce plasma-ketoconazole concentrations. Concentrations of isoniazid and rifampicin may also be reduced by ketoconazole.

Ketoconazole inhibits certain hepatic oxidase enzymes, especially the cytochrome P450 isoenzyme CYP3A4, in a similar way to itraconazole (p.537) and similar care should be taken to avoid adverse effects due to increased plasma concentrations of the interacting drugs.

A disulfiram-like reaction may occur in patients taking ketoconazole after drinking alcohol. The efficacy of oral contraceptives may be reduced.

◊ For reviews of drug interactions with azole antifungals, see Itraconazole, p.537.

Antimicrobial Action

Ketoconazole is an imidazole antifungal that interferes with ergosterol synthesis and therefore alters the permeability of the cell membrane of sensitive fungi. It is reported to be fungistatic at concentrations achieved clinically. Ketoconazole has a wide spectrum of antimicrobial activity including activity against *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Epidermophyton floccosum*, *Histoplasma capsulatum*, *Malassezia* spp., *Microsporum canis*, *Paracoccidioides brasiliensis*, *Trichophyton mentagrophytes*, and *T. rubrum*. Some strains of *Aspergillus* spp., *Cryptococcus neoformans*, and *Sporothrix schenckii* are sensitive.

Ketoconazole has activity against some Gram-positive bacteria and some antiprotozoal activity against *Leishmania* spp.

There are rare reports of *Candida albicans* acquiring resistance to ketoconazole.

Microbiological interactions. For the effect of imidazoles and amphotericin B on each other's antimicrobial activity, see Amphotericin B, p.525.

Resistance. For a discussion of increasing resistance of *Candida* spp. to azoles see Fluconazole, Antimicrobial Action, p.533.

Pharmacokinetics

The absorption of ketoconazole from the gastrointestinal tract is variable and increases with decreasing stomach pH. Mean peak plasma concentrations of about 3.5 micrograms/mL have been obtained 2 hours after an oral dose of 200 mg. Systemic absorption after topical or vaginal application in healthy subjects is minimal. Ketoconazole is more than 90% bound to plasma proteins, mainly albumin. It is widely distributed and appears in breast milk. Penetration into the CSF is poor. The elimination of ketoconazole is reported to be biphasic, with an initial half-life of 2 hours and a terminal half-life of about 8 hours.

Ketoconazole is metabolised in the liver to inactive metabolites. It is excreted as metabolites and unchanged drug chiefly in the faeces; some is excreted in the urine.

◊ References.

1. Daneshmend TK, Warnock DW. Clinical pharmacokinetics of ketoconazole. *Clin Pharmacokinet* 1988; **14:** 13–34.
2. Lelawongs P, *et al*. Effect of food and gastric acidity on absorption of orally administered ketoconazole. *Clin Pharm* 1988; **7:** 228–35.
3. Lake-Bakaar G, *et al*. Gastropathy and ketoconazole malabsorption in the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1988; **109:** 471–3.
4. Daneshmend TK. Diseases and drugs but not food decrease ketoconazole 'bioavailability'. *Br J Clin Pharmacol* 1990; **29:** 783–4.
5. Hurwitz A, *et al*. Gastric function in the elderly: effects on absorption of ketoconazole. *J Clin Pharmacol* 2003; **43:** 996–1002.

Uses and Administration

Ketoconazole is an imidazole antifungal used topically or orally. It is given orally in chronic mucocutaneous or vaginal candidiasis, in fungal infections of the gastrointestinal tract, in dermatophyte infections of the skin and fingernails not responding to topical treatment, and in systemic infections including blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis. It has been given for the prophylaxis of fungal infections in immunocompromised patients, although fluconazole or itraconazole are usually preferred. It has been recommended that, because of its erratic absorption and slow therapeutic response, ketoconazole should not be used for the treatment of life-threatening fungal infections, including fungal meningitis, or for severe infections in immunocompromised patients. Also, because of the risk of hepatotoxicity the use of ketoconazole in nonsystemic fungal infections tends to be restricted to serious infections resistant to other treatment.

The place of ketoconazole in the treatment of fungal infections is discussed in the various sections under Choice of Antifungal, p.517.

The usual oral dose for treatment and prophylaxis of fungal infections is 200 mg once daily taken with food. This may be increased to 400 mg daily if an adequate response is not obtained; in some infections even higher doses have been used. Children may be given about 3 mg/kg daily, or 50 mg for those aged 1 to 4 years and 100 mg for children aged 5 to 12 years. Treatment should usually be continued for 14 days and for at least