

one week after symptoms have cleared and cultures have become negative. Some infections may require several months of treatment and giving ketoconazole for such prolonged periods may increase the risk of hepatotoxicity.

A dose of 400 mg once daily for 5 days is used for the treatment of chronic vaginal candidiasis.

Ketoconazole is applied topically as a 2% cream in the treatment of candidal or dermatophyte infections of the skin, or in the treatment of pityriasis versicolor. It is used once or twice daily and continued for at least a few days after the disappearance of symptoms. A foam containing 2% ketoconazole applied twice daily for 4 weeks may be used in the treatment of seborrhoeic dermatitis. A shampoo containing 1 or 2% ketoconazole is also used; it is applied twice weekly for 2 to 4 weeks (or occasionally longer) in the treatment of dandruff or seborrhoeic dermatitis. The 2% shampoo is used once daily for up to 5 days in pityriasis versicolor. For prophylaxis of seborrhoeic dermatitis the 2% shampoo is used once every 1 to 2 weeks; for prophylaxis of pityriasis versicolor it may be used once daily for a maximum of 3 days before exposure to sunshine.

Acanthamoeba infections. Although there is currently no established treatment for granulomatous amoebic encephalitis, ketoconazole may have some activity against the *Acanthamoeba* spp. responsible for this infection and has been applied topically to skin lesions. Ketoconazole has also been suggested for *Acanthamoeba* keratitis (p.822), when it has been given orally with topical miconazole.

Acute respiratory distress syndrome. In two small double-blind, controlled trials,^{1,2} the development of acute respiratory distress syndrome (ARDS—p.1498) and mortality rates were lower in high-risk patients given ketoconazole than in those given placebo. An accompanying editorial³ commented that adequate blood concentrations appeared to be essential. The mode of action could be associated with inhibition of leukotriene and thromboxane synthesis.^{2,3} Nevertheless, in a study in 234 patients,⁴ ketoconazole failed to reduce mortality or improve clinical outcomes when given early in the course of ARDS. Some centres have developed guidelines for ketoconazole prophylaxis in patients at risk of ARDS.⁵

1. Slotman GJ, et al. Ketoconazole prevents acute respiratory failure in critically ill surgical patients. *J Trauma* 1988; **28**: 648–54.
2. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; **21**: 1635–42.
3. Slotman GJ. Ketoconazole: maybe it isn't the magic potion, but ... *Crit Care Med* 1993; **21**: 1642–4.
4. The ARDS Network Authors. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; **283**: 1995–2002.
5. Sinuff T, et al. Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; **14**: 1–6.

Blastomycosis. Ketoconazole has largely been replaced by itraconazole as the azole of choice in the treatment of blastomycosis (p.518) because of its higher incidence of adverse effects, and lower efficacy. If used as an alternative it is given in doses of 400 to 800 mg daily.¹

1. Chapman SW, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46**: 1801–12. Also available at: <http://www.journals.uchicago.edu/doi/pdf/10.1086/588300> (accessed 03/07/08)

Endocrine disorders and malignant neoplasms. Ketoconazole has been reported to impair steroid hormone synthesis¹ and to blunt the response of cortisone to adrenocorticotrophic hormone (ACTH)² and has been tried in the management of a number of endocrine disorders.

In **Cushing's syndrome** (p.2344), ketoconazole in doses of up to 1200 mg daily has been used successfully as an alternative or adjunct to definitive therapies such as surgery or radiotherapy.^{3–6}

Treatment of **hirsutism** is usually with an anti-androgen (see under Cypoterone, p.2089), but ketoconazole has been tried in small numbers of women at a dose of 300 mg daily⁷ or 400 mg daily,^{8,9} with variable results.

Ketoconazole has been reported to produce a beneficial response in some forms of **precocious puberty** (p.2081) that do not generally respond to gonadorelin analogues; cessation of menstruation and regression of pubertal signs in girls¹⁰ and reduced testosterone secretion and increase in adult height in boys^{11–13} has been noted in small numbers of patients studied.

The anti-androgenic effects of ketoconazole have also been found useful in the management of **prostatic cancer** (p.671) in selected patients,^{14–18} although there have been some concerns about its tolerability,¹⁷ and it is not generally used as a first-line treatment.

Ketoconazole was ineffective in suppressing **postoperative erection** in patients undergoing penile reconstructive surgery.¹⁹

1. Pont A, et al. Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med* 1982; **97**: 370–2.
2. White MC, Kendall-Taylor P. Adrenal hypofunction in patients taking ketoconazole. *Lancet* 1985; **i**: 44–5.
3. Winkling EW, et al. Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. *J Clin Oncol* 1995; **13**: 157–64.
4. Estrada J, et al. The long-term outcome of pituitary irradiation after unsuccessful transphenoidal surgery in Cushing's disease. *N Engl J Med* 1997; **336**: 172–7.
5. Berwaerts JJ, et al. Corticotropin-dependent Cushing's syndrome in older people: presentation of five cases and therapeutic use of ketoconazole. *J Am Geriatr Soc* 1998; **46**: 880–4.
6. Chou SC, Lin JD. Long-term effects of ketoconazole in the treatment of residual or recurrent Cushing's disease. *Endocr J* 2000; **47**: 401–6.
7. Venturoli S, et al. A prospective randomized trial comparing low dose flutamide, finasteride, ketoconazole, and cyproterone acetate-estrogen regimens in the treatment of hirsutism. *J Clin Endocrinol Metab* 1999; **84**: 1304–10.
8. Sonino N, et al. Low-dose ketoconazole treatment in hirsute women. *J Endocrinol Invest* 1990; **13**: 35–40.
9. Venturoli S, et al. Ketoconazole therapy for women with acne and/or hirsutism. *J Clin Endocrinol Metab* 1990; **71**: 335–9.
10. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. *J Pediatr Endocrinol Metab* 1999; **12**: 81–3.
11. Bertelloni S, et al. Long-term outcome of male-limited gonadotropin-independent precocious puberty. *Horm Res* 1997; **48**: 235–9.
12. Soriano-Guillén L, et al. Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. *J Clin Endocrinol Metab* 2005; **90**: 147–51.
13. Almeida MQ, et al. Oral treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. *Clin Endocrinol (Oxf)* 2008; **69**: 93–98.
14. Lowe FC, Bamberger MH. Indications for use of ketoconazole in management of metastatic prostate cancer. *Urology* 1990; **36**: 541–5.
15. Mahler C, et al. Ketoconazole and liarazole in the treatment of advanced prostatic cancer. *Cancer* 1993; **71**: 1068–73.
16. Small EJ, et al. Ketoconazole retains activity in advanced prostate cancer patients with progression despite flutamide withdrawal. *J Urol (Baltimore)* 1997; **157**: 1204–7.
17. Bok RA, Small EJ. The treatment of advanced prostate cancer with ketoconazole: safety issues. *Drug Safety* 1999; **20**: 451–8.
18. Pettaway CA, et al. Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol* 2000; **18**: 1050–7.
19. DeCastro BJ, et al. Oral ketoconazole for prevention of postoperative penile erection: a placebo controlled, randomized, double-blind trial. *J Urol (Baltimore)* 2008; **179**: 1930–2.

Hypercalcaemia. Ketoconazole has been used^{1,2} in the treatment of hypercalcaemia (p.1668). It acts to reduce 1,25-dihydroxycholecalciferol concentrations by inhibiting cytochrome P450-dependent 1 α -hydroxylation of vitamin D.

1. Yavuz H. Familial drugs for the treatment of hypercalcaemia. *J Pediatr* 1998; **133**: 311.
2. Young C, et al. Hypercalcaemia in sarcoidosis. *Lancet* 1999; **353**: 374.

Leishmaniasis. As discussed on p.824, ketoconazole has been tried as an alternative to conventional first- and second-line therapy for visceral leishmaniasis,^{1,2} although reports of treatment have not all been favourable.^{3,4}

It has also been tried in cutaneous leishmaniasis. A cure rate of 70% was reported in over 100 patients with *Leishmania major* infections treated with oral ketoconazole 200 to 400 mg daily for 4 to 6 weeks. Ketoconazole was not considered to be effective in infections due to *L. tropica*, *L. aethiopica*,⁵ or *L. guyanensis*.⁶ Ketoconazole 600 mg daily for 28 days has produced similar results to sodium stibogluconate intramuscularly for 20 days in patients with cutaneous leishmaniasis due to *L. panamensis*.⁷ A further comparative study⁸ of 96 patients being treated for cutaneous leishmaniasis, caused mainly by *L. major* or *L. tropica*, found ketoconazole given in doses of 600 mg in adults or 10 mg/kg in children for 30 days to be more effective than 6 to 8 bi-weekly intraleisional injections of meglumine antimonate. In another study,⁹ ketoconazole was less effective than sodium stibogluconate when cutaneous leishmaniasis was due to *L. braziliensis*, but more effective when *L. mexicana* was the cause.

1. Wali JP, et al. Ketoconazole in treatment of visceral leishmaniasis. *Lancet* 1990; **330**: 810–11.
2. Wali JP, et al. Ketoconazole in the treatment of antimony- and pentamidine-resistant Kala-azar. *J Infect Dis* 1992; **166**: 215–16.
3. Sundar S, et al. Ketoconazole in visceral leishmaniasis. *Lancet* 1990; **336**: 1582–3.
4. Rashid JR, et al. The efficacy and safety of ketoconazole in visceral leishmaniasis. *East Afr Med J* 1994; **71**: 392–5.
5. Weinrauch L, et al. Ketoconazole in cutaneous leishmaniasis. *Br J Dermatol* 1987; **117**: 666–7.
6. Dedet J-P, et al. Failure to cure *Leishmania braziliensis* guyanensis cutaneous leishmaniasis with oral ketoconazole. *Trans R Soc Trop Med Hyg* 1986; **80**: 176.
7. Saenz RE, et al. Efficacy of ketoconazole against *Leishmania braziliensis* panamensis cutaneous leishmaniasis. *Am J Med* 1990; **89**: 147–55.
8. Salmanpour R, et al. Comparative study of the efficacy of oral ketoconazole with intra-lesional meglumine antimonate (Glucontime) for the treatment of cutaneous leishmaniasis. *J Dermatol Treat* 2001; **12**: 159–62.
9. Navin TR, et al. Placebo-controlled clinical trial of sodium stibogluconate (Pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *J Infect Dis* 1992; **165**: 528–34.

Preparations

USP 31: Ketoconazole Oral Suspension; Ketoconazole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: C-86; Cetoni; Eumicel; Facion; Fangan; Fitonal; Fungicil; Grenfung; Keduo; Ketogel; Ketolef; Ketozol; Ketozol; Krol; Micoespex K; Micoral; Onifungal; Perative; Quadion; Socosep; Tersoderm Plus; Tik; Triatop; **Austral.:** Daktagold; Hexal Konazol Shampoo; Nizoral; Sebize; **Austria:** Fungal; Nizoral; **Belg.:** Docketoral; Nizoral; **Braz.:** Acidem; Arcolane; Candiderm; Candoral; Cetoconaf; Cetoconalab; Cetoheal; Cetomed; Cetomicros; Cetomizol; Cetonax; Cetoneo; Cetoni; Cetoni; Cetozan; Cetozaf; Cetozol; Fungal; Ketomical; Ketomizol; Ketozan; Lozan; Miconan; Micoral; Nizoral; Nizoretic; Noriderm; Noronal; Sicoconazol; Tona-zox; Zano; Zolmicol; **Canad.:** Ketoderm; Nizoral; **Chile:** Arcolane; Biogel; Eprofil; Fungarest; Fungum; Ketoni; Soriaderm; TKC; **Cz.:** Asquam; Nizoral; Orozanol; **Denm.:** Kezoral; Nizoral; **Fin.:** Nizoral; **Fr.:** Ketoderm; Ketolium; Nizoral; **Ger.:** Nizoral; Terzol; **Gr.:** Abba; Adenos; Aquanus; Botaderm; Cezolin; Ebersept; Flidaphen; Fungal; Ilgem; Libroman; Mycofebrin; Neo-egmol; Nyoxep; Scalpin; Sostatin; Valfusol; **Hong Kong:** Diazon; Fluzoral; Fungal; Ketozol; Ketozole; Lary; Nizoral; Pristine; Pristex; Sebizeol; Stada K; Syntrol; **Hung.:** Ketospor; Nizoral; **India:** Arcolane; Danfree; Danruf; Fungal; Fungicide; Hyphoral; Keto; **Indon.:** Anifunex; Dermaral; Dexazol; Dysfungal; Hexazol; Formyco; Funet; Fungal; Fungal; Interzol; Ketomed; Lusanoc; Micotium; Muzoral; Mycoderm; Mycoral; Mycozid; Nizol; Nizoral; Nofung; Picamic; Profungal; Solinfex; Sporex; Thicazol; Wizol; Zoloral; Zoralin; Zumasol; **Ir.:** Nizoral; **Israel:** Nizoral; **Ital.:** Nizoral; Triatop; **Malaysia:** Dezor; Fungal; Funginox; Ketozole; Kezoral; Lary; Nizoral; Pristine; Sebizeol; Sebizeol; Sebizeol; Yucomy; Ziconal; **Mex.:** Akorazol; Apo-Kesol; Bizoal; Conazol; Cremosan; Ergomicon; Eurolet; Fungipar; Fungal; Fungosine; Honzi; Keprobiozol; Kestomical; Ketofar; Ketomed; Ketomizol; Ketori; Konaderm; Konatril; Lemycil; Lizovag; Lornazol; Messelzol; Mi-Ke-Sons; Micozer; Micozol; Mycoden; Nastil; Nazol-farm; Nazoltec; Nizoral; Onofin-K; Prenalon; Remecon; Strizole; Termizol; Tinasil; Tiniazol; Tocomizol; Toconal; Tolcrem; Tomiko; Triatop; **Neth.:** Nizoral; **Norw.:** Fungal; Konazol; **NZ.:** Daktagold; Ketopine; Nizoral; Sebizeol; **Philipp.:** Ketovid; Nizoral; **Pol.:** Fungores; Nizoral; Noell; **Port.:** Farmorol; Frisof; Frisofal; Micopar; Nizale; Nizoral; Rapamic; Tedol; **Rus.:** Livalole (Ливалол); Mycosoral (Микосорал); Nizoral (Низорал); **S.Afr.:** Adco-Dermid; Ketazol; Kez; Nizreem; Nizoral; Nizorelle; Nizovules; Niz-shampoo; **Singapore:** Antanzol; Beatoconazole; Dezor; Dezoraf; Diazon; Ketozole; Kezoral; Nicozone; Nitazol; Nizoral; Pristine; Pristex; Profungal; Sebizeol; Yucomy; **Spain:** Fungarest; Fungo Farmasierra; Fungo Zeus; Keto-Cure; Ketoderma; Ketosidin; Medezol; Micotium; Panfungol; **Swed.:** Fundan; Fungal; Ketoson; **Switz.:** Ketozol; Nizoral; Terzol; **Thai.:** AC-FA; Chintara; Dezor; Diazon; Fungal; Fungiderm-K; Funginox; Kara; Katsin; Kazinal; Kenalyn; Kenazol; Kenazole; Kenoral; Ketazol; Ketazone; Ketocine; Ketolan; Ketomed; Ketonzole; Ketoraj; Ketosil; Ketozal; Kezon; Konazol; Lama; Lary; Manoket; Masarol; Mizoron; Mycella; Myco; Mycoral; Nizalol; Nizoral; Noraf; Pasalen; Sporaxyl; Sporoxyl; Triatop; **Turk.:** Fungal; Ketoral; Konazol; Nizoral; **UK:** Daktrin Gold; Dandraxol; Dandrid; Nizoral; **USA:** Extina; Nizoral; Xolegel; **Venez.:** Arcolane; Dan-free; Freetop; Kenazol; Ketazol; Ketocoval; Ketomed; Napox; Nizoral; Noractin; Topstarf.

Multi-ingredient: **Arg.:** Aeromicrosoma C; Bactisoda; Ciprocot; Der-cotex; Duo Minoxil; Gentacle; Gynenur; Ketohair; Linfol Dermico; Micozol Compuesto; Microsoma C; Ovogin; Prunisedan Biotici; Start NPI; Torgyn Duo; Tricur; Tridomala; Thieftel; **Braz.:** Betazol Cort; Candicort; Capel; Celocort; Cetobeta; Cetocort; Cetocorten; Cimecort; Emscort; Naderm; Novacort; Trok; Trok-N; **Chile:** KPL; **India:** Hyphoral; Scalp; **Ital.:** Keto Z; Ketomousse; **Malaysia:** Ketoplus; **Mex.:** Femisan; Gynoclin-V; Trexen Duo; **Philipp.:** Scalpex; **Rus.:** Keto Plus (Кето Плюс); **USA:** Xolegel Duo.

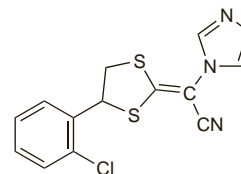
Lanoconazole (rINN)

Lanoconazol; Lanoconazolium; Latoconazole; NND-318; TJN-318. (\pm)- α -[(E)-4-(o-Chlorophenyl)-1,3-dithiolan-2-ylidene]imidazole-1-acetonitrile.

ЛАНКОНАЗОЛ

C₁₄H₁₀ClN₃S₂ = 319.8.

CAS — 101530-10-3.



Profile

Lanoconazole is an imidazole antifungal used topically in the treatment of fungal skin infections as a 1% cream, ointment, or solution, applied once daily. 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)

Jpn: Astat; **Port.:** Micoder.

Liranaftate (rINN)

Liranaftato; Liranaftatum; M-732; Piriteatrate. O-5,6,7,8-Tetrahydro-2-naphthyl 6-methoxy-N-methylthio-2-pyridinecarbamate.

Лиранафатат

C₁₈H₂₀N₂O₂S = 328.4.

CAS — 88678-31-3.