mycin Topical Solution; Sterile Erythromycin Ethylsuccinate; Sterile Erythromycin Gluceptate; Sterile Erythromycin Lactobionate.

Proprietary Preparations (details are given in Part 3)

Arg.: Algiderm; Ambamida; Atlamicin; Clarex; Eri; Erigrand; Erisine; Erisol; Erit; Eritroderm; Eritrofarm; Eritromed; Eryacne; Eryfluid; Etisux; Ilosone†; Iloticina†; Ingelets; Kitacne; Lederpax†; Oftalmolets; Pantomicina; Pentoclave; Stiemycin; Toperit; Trixne; Wemid; ***Austral.:*** E-Mycin; EES; Eryacne; Eryc; Eryhexal; Erythrocin; ***Austria:*** Akne Cordes; Aknemycin; Eryaknen; Erybesan; Eryhexal; Erystad; Erythrocin; Meromycin; Stiemycine; ***Belg.:*** Acneryne; Aknemycin; Eryderm†; Erythrocine; Erythroforte; Inderm; Stimycine; ***Braz.:*** Amplobid†; Eribiotic; Eriflogin†; Erimicina†; Eripan†; Eritax†; Eritrax†; Eritrex; Eritril†; Eritrin†; Eritrovit†; Eryacnen; Ilocin†; Ilosone; Kanazima; Lisotran†; Lisotrex†; Ortociclina†; Pantomicina; Rubromicin†; Siftrex†; Stiemycin; Valmicin; ***Canad.:*** Apo-Erythro; Diomycin†; EES; Erybid; Eryc; Erysol; Erythrocin†; Novo-Rythro; PCE; Staticin†; T-Stat†; ***Chile:*** Cinactiv; Eryacnen; Erypark; Gelerit; Labocne; Mercina; Pantomicina; ***Cz.:*** Aknefug-EL; Aknemycin; Emu-V†; Eryfluid; Erythrocin; Erythroskid†; Meromycin†; Monomycin†; ***Denm.:*** Abboticin; Erycin; Escumycin; Hexabotin; ***Fin.:*** Abboticin; Ermysin; ***Fr.:*** Abboticine; Egery; Ery; Eryacne; Eryfluid; Erythrocine; Erythrogel; Erythrogram†; Stimycine; ***Ger.:*** Akne Cordes†; Aknederm Ery; Aknefug-EL; Aknemycin; Ery; Ery-Diolan; Eryaknen; Erybeta; Erycinum; Erydermec; Eryhexal; Erysec; Erythro; Erythro-Hefa†; Erythrocin; Erythrogenat†; Hydrodermed; Inderm; InfectoMycin; Karex†; Monomycin†; Paediathrocin; Sanasepton; Stiemycine; ***Gr.:*** Acne Hermal; Dankit; Eryacne; Erycream†; Erygel; Erythrocin; Erythrogel†; Roug-Mycin†; ***Hong Kong:*** Aknemycin; Apo-Erythro; E-Mycin†; EES; Eryacne†; Erythro; Erythrocin; PCE†; Porphyrocin†; Stiemycin; ***Hung.:*** Aknefug-EL; Aknemycin; Eryc; Erythrotrop; Meromycin; ***India:*** Acnesol; Althrocin; Calthrox; E-Mycin; Eltocin; Erycin; Erycip; Erysafe; Erythrocin; Okamycin; ***Indon.:*** Cetathrocin; Corsatrocin; Duramycin; EES; Erphathrocin; Erycoat; Eryderm; Erymed; Erysanbe; Erythrin; Erythrocin; Jeracin; Opithrocin; Pharothrocin; ***Irl.:*** Erymax; Erythrocin; Erythroped; Primacine; Stiemycin; ***Israel:*** Acnetrim; Eryc†; Eryderm†; Erythro-Teva; Erythrocin; Erythroped†; ***Ital.:*** Eritrocina; Eryacne; Erytrociclin†; Lauromicina; ***Malaysia:*** Aknemycin; EES; Erogran†; Erotab†; Erycin; Eryderm; Eryped; Eryson; Erythrocin; Etrogran†; Etrotab†; Oftalmolosa Cusi; Sethro†; Stiemycin; ***Mex.:*** Apo-Trina; Benitrom; Bestocin; Biotril; Colitromin†; E-Trocima-P†; Eribec; Eriber; Erisuspen; Eritrerba†; Eritrofarmin†; Eritrolat; Eritropharma; Eritroquim†; Eritrosol; Eritrovier; Eritrowel; Eryacnen; Eryderm; Erylar; Examycin†; Iliocin; Ilosin; Ilosone; Iqfamicina; Latotryd; Lauricin; Laurimicina; Lauritran; Lederpax†; Optomicin; Pantomicina; Procephal; Promicin; Quimolauril; Sansacne; Stiemycin; T-Stat; Tropharma; Verytracin†; Witromin; ***Neth.:*** Aknemycin; Eryacne; Eryc†; Eryderm; Erythrocine; Erytrolyve; Inderm; Stiemycin; ***Norw.:*** Abboticin; Ery-Max; ***NZ:*** E-Mycin; EES; Era; Eryacne; Erythrocin; Stiemycin; ***Philipp.:*** Aldricin; Ery-Max; Erycar; Erythrocin; Fildrocin; Ilosone; Romaxin; Sansacne; Stiemycin; Upperzin; ***Pol.:*** Aknemycin; ***Port.:*** Akne-Mycin; Clinac; Eritina†; Eritrazon; Eritrocina; Eryc†; Eryfluid; ESE; ***S.Afr.:*** Acu-Erylate S; Betamycin; Emsyn†; Eromel†; Erycette; Eryderm; Erymycin; Erystat; Erythrocin; Erythroped†; Estomycin; Ilosone; Ilotycin TS; Purmycin; Rubimycin; Spectrasone; Stiemycin; Xeramel; ***Singapore:*** Aknemycin; EES; Ermycin†; Erotab; Eryacne; Eryderm; Eryped; Erysol†; Eryson; Erythrocin†; Ranthrocin; Stiemycin; T-Stat†; ***Spain:*** Bronsema; Denipil; Eridosis; Eritrogobens; Eritroveinte; Euskin; Lagarmicin; Lederpax; Loderm; Neo Iloticina†; Pantodrin†; Pantomicina; ***Swed.:*** Abboticin; Ery-Max; ***Switz.:*** Aknemycin; Aknilox; Erios; Eryaknen; Eryderm; Erythrocine; Inderm†; Karex†; Stiemycine†; ***Thai.:*** Elocin†; Erathrom; Ericin; Erimit; Erimycin; Ery-Tab; Eryacne; Erycin; Erycon; Erymin; Erysil; Eryth-mycin; Erythrocin; Etrola; Etrolate; Ilosone; Malocin; Pocin†; Redrocin; Rythocin; Servitrocin; Stacin; Stiemycin: Tomcin; ***Turk.:*** Aknilox; Erimicin; Eritro; Eritrosif; Eryacne; Erythrocin; ***UAE:*** Eromycin; ***UK:*** Erymax; Erythrocin; Erythroped; Rommix†; Stiemycin; Tiloryth; ***USA:*** Akne-Mycin; ATS; Del-Mycin; E-Base; E-Mycin; EES; Emgel†; Eramycin; Ery-Tab; Eryc†; Erycette; Eryderm; Erygel; Erymax†; Eryped; Erythrocin; Ilosone†; Ilotycin†; PCE; Robimycin Robitabs; Staticin†; T-Stat†; Theramycin Z†; ***Venez.:*** Eritimix†; Eritroped†; Eritrovac†; Eryacne; Ilosone; Iloticina†; Inderm; Laurimicina†; Leda-Rix; Pantomicina; Yisadin.

Multi-ingredient: ***Arg.:*** Acneout; Acnepas E; Benzamycin†; Clarex Compuesto; Ecnagel E; Erimicin; Eristin; Eritrobron; Kitacne AR†; Kitacne PB†; Pantomucol†; Pediazole†; Pentoclave Combi; Peroximicina; Stievamycin; Tratacne; Zineryt; ***Austria:*** Aknemycin compositum; Isotrexin; ***Belg.:*** Benzamycin; Zineryt; ***Braz.:*** Benzac Eritromicina†; Eritrex A; Isotrexin; ***Canad.:*** Benzamycin; Pediazole; Sans-Acne†; Stievamycin; ***Chile:*** Abboderm†; Benzac Plus; Benzamycin†; Bioquin; Dermodan Plus; Erimicin; Erylik; Pediazole†; Stievamycin; ***Cz.:*** Aknemycin Plus; Isotrexin; Zineryt; ***Fr.:*** Antibiotrex; Erylik; Pediazole; ***Ger.:*** Aknemycin; Aknemycin Plus; Clinesfar†; Ecolicin; Isotrexin; Synergomycin†; Zineryt; ***Gr.:*** Benzamycin†; Pediazole; ***Hong Kong:*** Benzamycin; Dermabaz†; Erylik; Pediazole†; ***Hung.:*** Isotrexin; Zineryt; ***Irl.:*** Benzamycin; Isotrexin; Zineryt; ***Israel:*** Aknemycin; Aknemycin Plus; Benzamycin; Pediazole; ***Ital.:*** Isotrexin; Lauromicina; Rubrociclina†; Zineryt; ***Malaysia:*** Aknemycin Plus; ***Mex.:*** Benzac Plus; Benzamycin; Bisolvon E; Eriwest; Pantobron; Pediazole; Quimobrom; Stievamycin; ***Neth.:*** Zineryt; ***NZ:*** Antibiotic Simplex; ***Philipp.:*** Elicocin; ***Pol.:*** Aknemycin Plus; Isotrexin; Zineryt; ***Port.:*** Isotrexin; Zineryt; ***Rus.:*** Zineryt (Зинерит); ***S.Afr.:*** Benzamycine†; Zineryt; ***Singapore:*** Aknemycin Plus; Benzamycin; Isotrexin; ***Spain:*** Bronsema Expectorante; Isotrex Eritromicina; Loderm Retinoico; Tosdiazina†; Zineryt; ***Switz.:*** Aknemycin; ***Thai.:*** Isotrexin; ***Turk.:*** Benzamycin; ***UK:*** Aknemycin Plus; Benzamycin†; Isotrexin; Zineryt; ***USA:*** Benzamycin; Eryzole†; Pediazole; ***Venez.:*** Pediazole†.

Ethambutol Hydrochloride

(BANM, USAN, rINNM)

CL-40881; Etambutol Hidroklorür; Etambutol-hidroklorid; Etambutolhydroklorid; Etambutolihydrokloridi; Etambutolio hidrochloridas; Etambutolu chlorowodorek; Éthambutol, chlorhydrate d'; Ethambutol-dihydrochlorid; Ethambutoli Dihydrochloridum; Ethambutoli hydrochloridum; Hidrocloruro de etambutol. (*S,S*)-*N,N'*-Ethylenebis(2-aminobutan-1-ol) dihydrochloride.

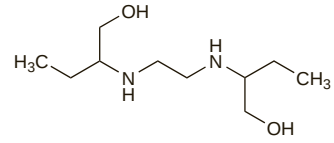
Этамбутола Гидрохлорид

$C_{10}H_{24}N_2O_2.2HCl$ = 277.2.

CAS — 74-55-5 (ethambutol); 1070-11-7 (ethambutol hydrochloride).

ATC — J04AK02.

ATC Vet — QJ04AK02.



(ethambutol)

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

Ph. Eur. 6.2 (Ethambutol Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. A 2% solution in water has a pH of 3.7 to 4.0. Store in airtight containers.

USP 31 (Ethambutol Hydrochloride). A white crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol; slightly soluble in chloroform and in ether.

Adverse Effects and Treatment

The most important adverse effect of ethambutol is retrobulbar neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, and green-red colour blindness. One or both eyes may be affected. The degree of visual impairment appears to depend on the dose and duration of therapy; toxicity is observed most frequently at daily doses of 25 mg/kg or more and after at least 2 months of therapy. Recovery of vision usually takes place over a period of a few weeks or months, but in rare cases it may take up to a year or more or the effect may be permanent. Retinal haemorrhage has occurred rarely.

Renal clearance of urate may be reduced and acute gout has been precipitated rarely.

Hypersensitivity reactions including skin rashes, pruritus, leucopenia, fever, and joint pains have occurred but appear to be rare with ethambutol. Other adverse effects which have been reported include confusion, disorientation, hallucinations, headache, dizziness, malaise, jaundice or transient liver dysfunction, peripheral neuropathy, thrombocytopenia, pulmonary infiltrates, eosinophilia, and gastrointestinal disturbances such as nausea, vomiting, anorexia, and abdominal pain.

Teratogenicity has been observed in *animals* (but see also Precautions, below).

Blood concentrations of ethambutol after overdosage may be reduced by haemodialysis or peritoneal dialysis.

Effects on the blood. Neutropenia has been reported in a patient on ethambutol, isoniazid, and rifampicin.[1] Each drug induced neutropenia individually on rechallenge. In another patient also receiving mixed antituberculous therapy, eosinophilia and neutropenia were associated with ethambutol; the effects recurred only on rechallenge with this drug.[2] Skin rash, blood eosinophilia, and pulmonary infiltrates occurred in a patient after 8 weeks of multidrug therapy for miliary tuberculosis. Rechallenge again attributed the adverse event to ethambutol.[3] Thrombocytopenia attributable to ethambutol has been reported in 2 patients.[4,5]

1. Jenkins PF, *et al*. Neutropenia with each standard antituberculosis drug in the same patients. *BMJ* 1980; **280:** 1069–70.
2. Wong CF, Yew WW. Ethambutol-induced neutropenia and eosinophilia. *Chest* 1994; **106:** 1638–9.
3. Wong PC, *et al*. Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement. *Eur Respir J* 1995; **8:** 866–8.
4. Rabinovitz M, *et al*. Ethambutol-induced thrombocytopenia. *Chest* 1982; **81:** 765–6.
5. Prasad R, Mukerji PK. Ethambutol-induced thrombocytopaenia. *Tubercle* 1989; **70:** 211–12.

Effects on the CNS. A 40-year-old man with advanced HIV infection taking oral ethambutol for *Mycobacterium avium* complex infection had rapid cognitive decline, hallucinations, and delusions within 2 weeks of starting ethambutol treatment; symptoms resolved on stopping treatment.[1]

1. Martin SJ, Bowden FJ. Ethambutol toxicity manifesting as acute onset psychosis. *Int J STD AIDS* 2007; **18:** 287–8.

Effects on the eyes. A review[1] on the ocular toxicity of ethambutol reported that when ethambutol is taken for more than 2 months the incidence of retrobulbar neuritis is about 18% in patients receiving a daily dose of more than 35 mg/kg, reducing to 5 to 6% with a daily dose of 25 mg/kg, and less than 1% with a daily dose of 15 mg/kg. An earlier study reported ophthalmic effects in 10 of 2184 patients receiving ethambutol in doses of 25 mg/kg or less daily, although few of the 10 patients complained of symptoms.[2] In 9 of the 10 patients, ocular changes occurred after the second month of treatment. In the 928 patients who only received 2 months of ethambutol therapy, ocular toxicity was not reported. A prospective study[3] of 229 patients taking ethambutol for *Mycobacterium avium* complex lung disease reported that ocular toxicity was more common in patients given daily doses rather than intermittent (3 times a week) therapy.

While short-term use of ethambutol is usually safe, deterioration of vision leading to long-term blindness has been reported after only a few doses of ethambutol;[4] it was suspected that this was an idiosyncratic reaction. Rapid onset reversible ocular toxicity has also occurred.[5]

Visual defects occurring with ethambutol generally resolve when the drug is stopped.

1. Chan RYC, Kwok AKH. Ocular toxicity of ethambutol. *Hong Kong Med J* 2006; **12:** 56–60.
2. Citron KM, Thomas GO. Ocular toxicity from ethambutol. *Thorax* 1986; **41:** 737–9.
3. Griffith DE, *et al*. Ethambutol ocular toxicity in treatment regimens for Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2005; **172:** 250–3.
4. Karnik AM, *et al*. A case of ocular toxicity to ethambutol—an idiosyncratic reaction? *Postgrad Med J* 1985; **61:** 811–13.
5. Schild HS, Fox BC. Rapid-onset reversible ocular toxicity from ethambutol therapy. *Am J Med* 1991; **90:** 404–6.

Effects on the kidneys. Interstitial nephritis has been reported[1,2] in 5 patients receiving ethambutol and isoniazid; 3 were also receiving additional antimycobacterials. In another patient, acute renal failure occurred secondary to interstitial nephritis which was thought to have been induced by ethambutol.[3]

1. Collier J, *et al*. Two cases of ethambutol nephrotoxicity. *BMJ* 1976; **2:** 1105–6.
2. Stone WJ, *et al*. Acute diffuse interstitial nephritis related to chemotherapy of tuberculosis. *Antimicrob Agents Chemother* 1976; **10:** 164–72.
3. García-Martín F, *et al*. Acute interstitial nephritis induced by ethambutol. *Nephron* 1991; **59:** 679–80.

Effects on the liver. Although transient abnormalities in liver function commonly occur during the early stages of antituberculosis treatment, drugs other than ethambutol are generally considered responsible. Ethambutol has generated fewer reports of hepatotoxicity to the UK CSM than rifampicin, isoniazid, or pyrazinamide,[1] and the use of regimens containing ethambutol has been recommended for patients unable to tolerate standard regimens due to hepatotoxicity.[1-3]

1. Ormerod LP, *et al*. Hepatotoxicity of antituberculosis drugs. *Thorax* 1996; **51:** 111–13.
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53:** 536–48. [Although these guidelines were replaced by ones issued by NICE in 2006 the latter do not *"explain tuberculosis or its treatment in detail"* and therefore reference to the earlier guidelines has been retained] Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/Chemotherapy.pdf (accessed 29/07/08)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 03/10/07) Correction. *ibid*. 2005: **53:** 1203. [dose]

Effects on the skin. Toxic epidermal necrolysis[1] and lichenoid[2] and erythema multiforme-type drug eruptions[3] have been associated with the use of ethambutol. Delayed hypersensitivity reactions have also been reported.[4] Licensed product information notes that Stevens-Johnson syndrome and dermatitis have also occurred.

1. Pegram PS, *et al*. Ethambutol-induced toxic epidermal necrolysis. *Arch Intern Med* 1981; **141:** 1677–8.
2. Grossman ME, *et al*. Lichenoid eruption associated with ethambutol. *J Am Acad Dermatol* 1995; **33:** 675–6.
3. Kurokawa I, *et al*. Erythema multiforme-type drug eruption due to ethambutol with eosinophilia and liver dysfunction. *Int J Antimicrob Agents* 2003; **21:** 596–7.
4. Bakkum RSLA, *et al*. Delayed-type hypersensitivity reaction to ethambutol and isoniazid. *Contact Dermatitis* 2002; **46:** 359.

Hyperuricaemia. In a controlled study of 71 patients receiving ethambutol 20 mg/kg daily orally with other antimycobacterials, serum-uric acid concentrations increased in 66, mainly in the first 2 weeks of treatment.[1] One patient experienced arthralgia and another acute gouty arthritis. Serum-uric acid concentrations did not change in 60 control patients receiving other antimycobacterials.

1. Khanna BK, Gupta VP. Ethambutol-induced hyperuricaemia. *Tubercle* 1984; **65:** 195–9.

Precautions

Ethambutol is generally contra-indicated in patients with optic neuritis. It should be used with great care in patients with visual defects, the elderly, and in children in whom evaluation of changes in visual acuity may be difficult (see also Children, below). Ocular examination is recommended before treatment with ethambutol and some consider that regular examinations are necessary during treatment, especially in children. Patients should be advised to report visual disturbances imme-

diately and to stop ethambutol pending visual evaluation.

Ethambutol should be given in reduced dosage to patients with renal impairment and dosage adjustments may need to be made according to serum concentrations. The *BNF* recommends peak concentrations of 2 to 6 mg/L and trough concentrations of less than 1 mg/L.

Ethambutol may precipitate attacks of gout.

Although ethambutol crosses the placenta and may be teratogenic in *animals*, problems in humans have not been documented. It is generally considered that the benefits of ethambutol in the treatment of tuberculosis outweigh any potential risks in pregnancy.

Breast feeding. Ethambutol distributes into breast milk to produce concentrations similar to those in plasma. However, no adverse effects have been seen in breast-fed infants whose mothers were receiving ethambutol, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. 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 03/10/07)

Children. Due to the possible difficulty of evaluating changes in visual acuity that may be induced in children receiving ethambutol, the *BNFC* advises that it should be used with caution in children under 5 years of age and unable to report visual changes accurately, whereas in the USA licensed product information has advised against use in those under 13 years of age.

The authors of a review of the use of ethambutol in children concluded that no extra precautions were necessary in children aged 5 years or more, and that it could also be used in younger children without undue fear of adverse effects.[1] Another review suggested that visual toxicity is not a particular problem except perhaps when CNS infection is involved.[2] A literature review[3] on the use of ethambutol in children reported almost no ocular toxicity at daily doses of 15 to 30 mg/kg. Ethambutol is therefore considered safe in children of all ages at a daily dose of 20 mg/kg (range 15 to 25 mg/kg) or a three times weekly dose of 30 mg/kg.

1. Trébucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *Int J Tuberc Lung Dis* 1997; **1:** 12–15.
2. Graham SM, *et al*. Ethambutol in tuberculosis: time to reconsider? *Arch Dis Child* 1998; **78:** 274–8.
3. WHO. *Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children*. Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.365_eng.pdf (accessed 03/10/07)

Antimicrobial Action

Ethambutol is active against *Mycobacterium tuberculosis* and some other mycobacteria. Resistant strains of *M. tuberculosis* are readily produced if ethambutol is used alone.

Pharmacokinetics

About 80% of an oral dose of ethambutol is absorbed from the gastrointestinal tract. Absorption is not significantly impaired by food (but see also Bioavailability, below). After a single dose of 25 mg/kg peak plasma concentrations of up to 5 mg/L appear within 4 hours, and are less than 1 mg/L by 24 hours.

Ethambutol is distributed to most tissues, including the lungs, kidneys, and erythrocytes. About 10 to 50% may diffuse into the CSF when the meninges are inflamed. It has been reported to cross the placenta and is distributed into breast milk. The elimination half-life after oral doses is about 3 to 4 hours.

Ethambutol is partially metabolised in the liver to the aldehyde and dicarboxylic acid derivatives which are inactive and then excreted in the urine. Most of a dose appears in the urine within 24 hours as unchanged drug and 8 to 15% as the inactive metabolites. About 20% of the dose is excreted unchanged in the faeces.

Bioavailability. Although the absorption of ethambutol is not generally regarded as being impaired by food, a study in 14 healthy subjects[1] suggested that giving it with a high-fat meal or an antacid could delay absorption and reduce the maximum plasma concentration.

1. Peloquin CA, *et al*. Pharmacokinetics of ethambutol under fasting conditions, with food, and with antacids. *Antimicrob Agents Chemother* 1999; **43:** 568–72.

HIV-infected patients. Malabsorption of ethambutol and other antituberculous drugs may occur in patients with HIV infection and tuberculosis, and may contribute to acquired drug resistance and reduced efficacy of tuberculosis treatment. For further information on the absorption of antituberculous drugs in HIV-infected patients see under Rifampicin, p.328.

Pregnancy and breast feeding. Ethambutol crosses the placenta and is present in fetal tissue in amounts of at least 74.5% of the maternal serum concentration.[1] Ethambutol distributes into breast milk to produce concentrations similar to those in plasma.[2]

1. Holdiness MR. Transplacental pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1987; **13:** 125–9.
2. Snider DE, Powell KE. Should women taking antituberculosis drugs breast-feed? *Arch Intern Med* 1984; **144:** 589–90.

Uses and Administration

Ethambutol is used with other antituberculous drugs in the primary treatment of pulmonary and extrapulmonary tuberculosis (p.196) to suppress emergence of resistance to the other drugs used in the regimens. It is also used as a component of regimens for the treatment of nontuberculous mycobacterial infections (p.181).

In the treatment of tuberculosis, ethambutol is given, as the hydrochloride, usually with isoniazid, rifampicin, and pyrazinamide in the initial 8-week phase and sometimes in the continuation phase. It is given orally in a single daily dose of 15 mg/kg, or 30 mg/kg three times weekly. Initial doses of ethambutol 25 mg/kg daily for 60 days may be given to patients who have previously had antimycobacterial therapy, reduced to 15 mg/kg daily thereafter.

For details of doses in infants, children, and adolescents, see below. If it is used in patients with renal impairment, doses should be adjusted according to serum concentrations (see Precautions, above).

Fixed-dose combination products have been developed in order to improve patient compliance and avoid monotherapy, thereby decreasing the risk of acquired drug resistance. Combination products containing ethambutol with isoniazid, isoniazid and rifampicin, and isoniazid, rifampicin, and pyrazinamide are available in some countries.

Administration in children. For the treatment of *drug-resistant* tuberculosis in infants, children, and adolescents the American Academy of Pediatrics suggests a dose of ethambutol 15 to 25 mg/kg daily or 50 mg/kg twice weekly (to a maximum of 2.5 g) by mouth.

For *congenitally acquired* tuberculosis in neonates the *BNFC* suggests a dose of 15 mg/kg once daily. For the treatment of children 1 month and older a dose of 15 mg/kg once daily or 30 mg/kg three times a week for the 2 month initial treatment phase is suggested.

See also Children, under Precautions above

Preparations

BP 2008: Ethambutol Tablets;
USP 31: Ethambutol Hydrochloride Tablets; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Myambutol; ***Austria:*** Etibi; Myambutol; ***Belg.:*** Myambutol; ***Canad.:*** Etibi; ***Cz.:*** Sural; ***Denm.:*** Myambutol; ***Fin.:*** Oributol; ***Fr.:*** Myambutol; ***Ger.:*** EMB; Myambutol; ***Gr.:*** Dexambutol; Myambutol; ***Hong Kong:*** EMB; Myambutol†; ***Hung.:*** Sural; ***India:*** Combutol; Myambutol; Mycobact; Mycobutol; Rifacom E-Z; Themibutol; Tibitol; ***Indon.:*** Arsitam; Bacbutol; Cetabutol; Corsabutol; ETH Ciba; Parabutol; Santibi; Tibigon; Tibitol; ***Ital.:*** Etapiam; Miambutol; ***Mex.:*** Apo-Probutol†; Dovalem; Myambutol†; Tambutec; ***Neth.:*** Myambutol; ***NZ:*** Myambutol; ***Philipp.:*** Danbutol; Odetol; ***Port.:*** Turresis; ***Rus.:*** Ebutol (Эбутол); Ethambusin (Этамбусин)†; Upbutol (Апбутол); ***S.Afr.:*** Purderal; ***Singapore:*** E-Butol; ***Spain:*** Myambutol; ***Swed.:*** Myambutol; ***Switz.:*** Myambutol; ***Thai.:*** Conbutol†; Etham; Ethbutol; Lambutol; Myambutol†; Myrin-P; Myrin†; Servambutol; Tobutol; ***Turk.:*** Miambutol; ***USA:*** Myambutol.

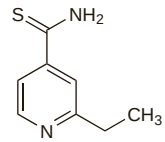
Multi-ingredient: ***Austria:*** Myambutol-INH; ***Denm.:*** Rimstar; ***Fin.:*** Rimstar; ***Ger.:*** EMB-INH†; Myambutol-INH; ***India:*** Akt-3; Akt-4; Bicox-E†; Combunex; Coxina-3; Coxina-4; Cx-4; Cx-5; Gocox-4†; Inabutol Forte; Myconex; RHZ-Plus; Rifa E; Wokex-3; Wokex-4; Xeed-3E; Xeed-4; ***Indon.:*** bacbutINH; Erabutol Plus; Meditam-6; Mycothambin-INH; Niazitol; Pulna; Rimstar; Santibi Plus; ***Ital.:*** Etanicozid B6; Miazide B6†; ***Mex.:*** Myambutol-INH†; ***Philipp.:*** 4D; Continukit; Continukit Plus; Econokit; Econokit-MDR; Ethamizid; Ethi 400; Fixcom 3; Fixcom 4; Myrin; Myrin-P; Quadtab; Rimstar; Sthamizide; SVM-Polypac-A; Tres; Tritab; Viper; ***Rus.:*** Isocomb (Изокомб); Lomecomb (Ломекомб); Phthizoetham (Фтизоэтам); Protiocomb (Протиокомб); Repin B (Репин В); Rimstar 4-FDC (Римстар 4-ФДС); ***S.Afr.:*** Myrin Plus†; Myrin†; Rifafour; Rimstar; ***Spain:*** Rimstar; ***Swed.:*** Rimstar; ***Switz.:*** Myambutol-INH†; ***Thai.:*** Rifafour; Rimstar.

Ethionamide *(BAN, USAN, rINN)*

Ethionamid; Éthionamide; Ethionamidum; 2-Ethylthioisonicotinamide; Etionamid; Etionamida; Etionamidas; Etionamide; Etionamidi; 1314-TH. 2-Ethylpyridine-4-carbothioamide.

Этионамид

$C_8H_{10}N_2S$ = 166.2.
CAS — 536-33-4.
ATC — J04AD03.
ATC Vet — QJ04AD03.



Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Ethionamide). Small yellow crystals or a yellow crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in methyl alcohol.
USP 31 (Ethionamide). A bright yellow powder having a faint to moderate sulfide-like odour. Slightly soluble in water, in chloroform, and in ether; sparingly soluble in alcohol and in propylene glycol; soluble in methyl alcohol. pH of a 1% slurry in water is between 6.0 and 7.0. Store in airtight containers.

Adverse Effects and Treatment

Many patients cannot tolerate therapeutic doses of ethionamide and have to stop treatment. The most common adverse effects are dose-related gastrointestinal disturbances, including nausea, vomiting, diarrhoea, anorexia, excessive salivation, a metallic taste, stomatitis, and abdominal pain. Tolerance may be improved by reducing the dose, adjusting the timing of dosage, or giving an antiemetic.

Mental disturbances including depression, anxiety, and psychosis have been provoked. Dizziness, drowsiness, headache, postural hypotension, and asthenia may also occur occasionally. Peripheral and optic neuropathy, diplopia and blurred vision, and a pellagra-like syndrome have occurred. Pyridoxine or nicotinamide have been suggested for the treatment or prevention of neurotoxic effects. Hepatitis may occur occasionally, with or without jaundice. The incidence of hepatotoxicity is increased when ethionamide is given with rifampicin.

Other adverse effects reported include hypersensitivity reactions, thrombocytopenia and purpura, alopecia, dermatitis (including photodermatitis), endocrine disturbances, hypoglycaemia, and hypothyroidism with or without goitre.

Teratogenic effects have been reported in *animals*.

Effects on the liver. Use of ethionamide or protionamide with rifampicin for the treatment of multibacillary leprosy has been associated with a high incidence of hepatotoxicity. A hepatitis incidence of 4.5 to 5% has been reported for patients on ethionamide or protionamide, rifampicin, and either dapsone or clofazimine.[1,2] In these studies, diagnosis of hepatitis was based on clinical assessment. When laboratory monitoring was used, an incidence of 13% was reported with a regimen of ethionamide or protionamide with rifampicin and dapsone.[3] A regimen of protionamide, dapsone, rifampicin, and clofazimine has been associated with a 22% incidence based on laboratory monitoring.[4] Use of ethionamide with pyrazinamide has also resulted in a high incidence of abnormal liver function tests.[5]

In the above studies rifampicin was given daily during part or all of the regimens. The incidence of hepatotoxicity when ethionamide or protionamide is used with once-monthly rifampicin may be lower; hepatotoxicity was not reported in patients receiving monthly rifampicin and daily protionamide, isoniazid, and dapsone.[6]

1. Pattyn SR, *et al*. Hepatotoxicity of the combination of rifampin-ethionamide in the treatment of multibacillary leprosy. *Int J Lepr* 1984; **52:** 1–6.
2. Pattyn SR, *et al*. Combined regimens of one year duration in the treatment of multibacillary leprosy—II: combined regimens with rifampicin administered during 6 months. *Lepr Rev* 1989; **60:** 118–23.
3. Cartel J-L, *et al*. Hepatitis in leprosy patients treated by a daily combination of dapsone, rifampin, and a thioamide. *Int J Lepr* 1983; **51:** 461–5.
4. Ji B, *et al*. Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy. *Lepr Rev* 1984; **55:** 283–9.
5. Schless JM, *et al*. The use of ethionamide in combined drug regimens in the re-treatment of isoniazid-resistant pulmonary tuberculosis. *Am Rev Respir Dis* 1965; **91:** 728–37.
6. Ellard GA, *et al*. Long-term prothionamide compliance: a study carried out in India using a combined formulation containing prothionamide, dapsone and isoniazid. *Lepr Rev* 1988; **59:** 163–75.

Precautions

Ethionamide should not be used in severe hepatic impairment. Liver function tests should be carried out before, and regularly during, treatment with ethionamide.

Caution is necessary in patients with depression or other psychiatric illness. Difficulty may be experienced in the management