Erythromycin Lactobionate *(BANM, rINNM)*

Eritromicin-laktobionát; Eritromicino laktobionatas; Érythromycine, lactobionate d'; Erythromycini lactobionas; Erythromycin-laktobionát; Erytromycinlaktobionat; Erytromycyny laktobionian; Erytromysiinilaktov; Éthylèneglycol, monostéarate d'; Lactobionato de eritromicina; Lactobionato de eritromicina. Erythromycin mono(4-*O*-β-D-galactopyranosyl-D-gluconate).

Эритромицина Лактобионат

$C_{37}H_{67}NO_{13}.C_{12}H_{22}O_{12}$ = 1092.2.

CAS — 3847-29-8.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

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

Ph. Eur. 6.2 (Erythromycin Lactobionate). Salt of a product obtained by fermentation using a strain of *Streptomyces erythreus*. White or slightly yellow, hygroscopic powder. Soluble in water; freely soluble in dehydrated alcohol and in methyl alcohol; very slightly soluble in acetone and in dichloromethane. A 2% solution in water has a pH of 6.5 to 7.5. Store in airtight containers.

USP 31 (Sterile Erythromycin Lactobionate). It has a potency equivalent to not less than 525 micrograms of erythromycin per mg, calculated on the anhydrous basis. pH of a solution in water containing the equivalent of erythromycin 5% is between 6.5 and 7.5.

Erythromycin Propionate *(BANM, USAN, rINNM)*

Erythromycin Propanoate; Érythromycine, Propionate d'; Erythromycini Propionas; Propionato de eritromicina; Propionylerythromycin. Erythromycin 2′-propionate.

Эритромицина Пропионат

$C_{40}H_{71}NO_{14}$ = 790.0.

CAS — 134-36-1.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

Pharmacopoeias. In *Fr.*

Erythromycin Stearate *(BANM, rINNM)*

Eritromicino stearatas; Eritromicin-sztearát; Eritromisin Stearat; Érythromycine, stéarate d'; Erythromycini stearas; Erythromycin-stearát; Erytromycinstearat; Erytromycyny stearynian; Erytromysiinistearaatti; Estearato de eritromicina. Erythromycin octadecanoate.

Эритромицина Стеарат

$C_{37}H_{67}NO_{13}.C_{18}H_{36}O_2$ = 1018.4.

CAS — 643-22-1.

ATC — D10AF02; J01FA01; S01AA17.

ATC Vet — QD10AF02; QJ01FA01; QS01AA17.

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

Ph. Eur. 6.2 (Erythromycin Stearate). A mixture of the stearates of erythromycin and stearic acid. A white or almost white crystalline powder. Practically insoluble in water; soluble in acetone and in methyl alcohol. Solutions may be opalescent.

USP 31 (Erythromycin Stearate). The stearic acid salt of erythromycin with an excess of stearic acid. White or slightly yellow crystals or powder, odourless or may have a slight, earthy odour. Practically insoluble in water; soluble in alcohol, in chloroform, in ether, and in methyl alcohol. Store in airtight containers.

Incompatibility and stability. The stability of erythromycin derivatives is dependent upon pH, with particularly rapid degradation occurring at a pH greater than 10 or less than 5.5. Incompatibility might reasonably be expected, therefore, when erythromycin preparations are mixed with drugs or preparations that have a highly acidic or alkaline pH. In practice, reports of incompatibility are not always consistent, and other factors such as the temperature and concentration of solutions, and the diluents used, may play a role.

Solutions for infusion. For the preparation of solutions of erythromycin lactobionate for infusion, a primary solution containing not more than 5% of erythromycin should be prepared first; only water for injection should be used in preparing the primary solution. It should be further diluted with sodium chloride 0.9% or other suitable intravenous fluid before use. Acidic solutions, such as glucose, should only be used if neutralised with sodium bicarbonate.

Adverse Effects

Erythromycin and its salts and esters are generally well tolerated and serious adverse effects are rare. Gastrointestinal disturbances such as abdominal discomfort and cramp, nausea, vomiting, and diarrhoea are fairly common after both oral and parenteral use, probably because of the stimulant activity of erythromycin on the gut. Gastrointestinal effects are dose related and appear to be more common in young than in older patients. Superinfection with resistant organisms may occur and pseudomembranous colitis has been reported.

Hypersensitivity reactions appear to be uncommon, having been reported in about 0.5% of patients, and include pruritus, urticaria, and skin rash as well as occasional cases of anaphylaxis. Stevens-Johnson syndrome and toxic epidermal necrolysis have also been reported very rarely. Hypersensitivity or irritation may occur after topical application of erythromycin.

A hypersensitivity reaction is thought to be responsible for the hepatotoxicity sometimes reported in patients receiving erythromycin or its derivatives but this has been disputed by some. Most reports of cholestatic hepatitis have been in patients receiving the estolate, and it has been suggested that the propionyl ester linkage is particularly associated with hepatotoxicity, but symptoms have also been reported in patients given the base and most of the other derivatives, both orally and parenterally. Symptoms indicative of cholestasis, including upper abdominal pain (sometimes very severe), nausea and vomiting, abnormal liver function values, raised serum bilirubin, and usually jaundice, may be accompanied by rash, fever, and eosinophilia. Symptoms usually occur in patients who have been taking the drug for more than 10 days, although they may develop more quickly in patients given the drug previously. Hepatic dysfunction seems to be rare in children under 12 years of age. The effects of erythromycin on the liver are generally reversible on stopping treatment. Erythromycin may interfere with tests for serum aspartate aminotransferase, which might make diagnosis of hepatotoxicity more difficult.

A generally reversible sensorineural deafness, sometimes with tinnitus, has been reported in patients given erythromycin and appears to be related to serum concentration, with an increased likelihood of such effects in patients given doses of 4 g or more daily of base or its equivalent, in those given intravenous therapy, and in those with renal or hepatic impairment.

Other adverse effects that have been reported in patients given erythromycin include agranulocytosis, aggravation of muscular weakness in myasthenia gravis patients, and pancreatitis. Prolongation of the QT interval and other arrhythmias, sometimes fatal, including torsade de pointes have been reported particularly with intravenous use. There have also been isolated reports of transient CNS adverse effects including confusion, hallucinations, seizures, and vertigo.

Parenteral formulations of erythromycin are irritant and intravenous dosage may produce thrombophlebitis, particularly at high doses. Intramuscular injection is generally avoided as it may produce severe pain.

◊ General reviews.

1. Periti P, *et al.* Adverse effects of macrolide antibacterials. *Drug Safety* 1993; **9:** 346–64.
2. Principi N, Esposito S. Comparative tolerability of erythromycin and newer macrolide antibacterials in paediatric patients. *Drug Safety* 1999; **20:** 25–41.
3. Rubinstein E. Comparative safety of the different macrolides. *Int J Antimicrob Agents* 2001; **18** (suppl 1): S71–S76.

Effects on body temperature. A report of hypothermia associated with oral erythromycin in 2 children.[1] Symptoms resolved on stopping the drug. The children were cousins, perhaps indicating a genetic predisposition to the effect. There has also been a similar report of hypothermia in 3 children given azithromycin orally.[2]

1. Hassel B. Hypothermia from erythromycin. *Ann Intern Med* 1991; **115:** 69–70.
2. Kavukçu S, *et al.* Hypothermia from azithromycin. *J Toxicol Clin Toxicol* 1997; **35:** 225 6.

Effects on the cardiovascular system. There have been several reports[1-6] of QT prolongation or torsade de pointes associated with erythromycin, particularly with intravenous use.

A review[7] of reports of torsade de pointes received by the FDA Adverse Event Reporting System between 1987 and December 2000 identified 156 cases associated with use of the macrolides azithromycin, clarithromycin, dirithromycin, or erythromycin. Of these reports, half involved the use of other drugs known to prolong the QT interval; co-morbid diseases and physiological abnormalities, including cardiac abnormalities, were also commonly reported. A retrospective analysis[8] of a cohort of patients who suffered sudden death from cardiac causes found that the rate of sudden cardiac death was twice as high among current users of erythromycin as in those not using antibacterials; there was no such increase among former users, nor among current users of amoxicillin. The greatest increase in risk was seen in patients using erythromycin with inhibitors of the cytochrome P450 isoenzyme subfamily CYP3A; such patients had more than 5 times the risk of sudden cardiac death of patients who took neither.

1. McComb JM, *et al.* Recurrent ventricular tachycardia associated with QT prolongation after mitral valve replacement and its association with intravenous administration of erythromycin. *Am J Cardiol* 1984; **54:** 922–3.
2. Schoenenberger RA, *et al.* Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsades de pointes). *BMJ* 1990; **330:** 1375–6.
3. Nattel S, *et al.* Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiologic mechanism. *Am J Med* 1990; **89:** 235–8.
4. Gitler B, *et al.* Torsades de pointes induced by erythromycin. *Chest* 1994; **105:** 368–72.
5. Gouyon JB, *et al.* Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 1994; **13:** 840–1.
6. Drici M-D, *et al.* Cardiac actions of erythromycin: influence of female sex. *JAMA* 1998; **280:** 1774–6.
7. Shaffer D, *et al.* Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. *Clin Infect Dis* 2002; **35:** 197–200.
8. Ray WA, *et al.* Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; **351:** 1089–96.

Effects on the gastrointestinal tract. Comparison in patients with upper respiratory-tract infections has suggested that erythromycin ethyl succinate may be associated with less abdominal pain than an equivalent dosage of erythromycin base.[1] Another study has indicated that there was no significant difference in gastrointestinal symptoms between plain and enteric-coated formulations of erythromycin base.[2] Severe nausea and vomiting after rapid intravenous infusion of erythromycin lactobionate stopped in 2 patients who transferred to oral erythromycin base or ethyl succinate.[3] However, the adverse effects may have been due to the rate of infusion, since in 2 further patients symptoms resolved when the lactobionate was given more slowly as a more dilute solution.[3]

There have been a number of studies suggesting an association between erythromycin and infantile hypertrophic pyloric stenosis.[4-6] A retrospective cohort study of 469 infants who had received erythromycin found that 43 were diagnosed with the condition including 36 male infants, although erythromycin had been prescribed almost equally for males and females.[5] All the infants in whom stenosis developed were given erythromycin in the first 2 weeks of life. In another study,[6] involving 7138 infants who received erythromycin between 3 and 90 days of life, use of the drug between 3 and 13 days of life was associated with an almost eightfold increased risk of infantile hypertrophic pyloric stenosis. However, it was believed that the evidence did not support a generalisation of this association to the whole class of macrolides[7] although pyloric stenosis has been reported in breast-fed infants associated with the use of erythromycin or several other macrolides in their mothers (see under Precautions, below).

For reference to the stimulant effects of erythromycin on the gastrointestinal tract, see Decreased Gastrointestinal Motility under Uses and Administration, below.

1. Saloranta P, *et al.* Erythromycin ethylsuccinate, base and acistrate in the treatment of upper respiratory tract infection: two comparative studies of tolerability. *J Antimicrob Chemother* 1989; **24:** 455–62.
2. Ellsworth AJ, *et al.* Prospective comparison of patient tolerance to enteric-coated vs non-enteric-coated erythromycin. *J Fam Pract* 1990; **31:** 265–70.
3. Seifert CF, *et al.* Intravenous erythromycin lactobionate-induced severe nausea and vomiting. *DICP Ann Pharmacother* 1989; **23:** 40–4.
4. Honein MA, *et al.* Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet* 1999; **354:** 2101–5. Correction. *ibid.* 2000; **355:** 758.
5. Mahon BE, *et al.* Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. *J Pediatr* 2001; **139:** 380–4.
6. Cooper WO, *et al.* Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med* 2002; **156:** 647–50.
7. Hauben M, Amsden GW. The association of erythromycin and infantile hypertrophic pyloric stenosis: causal or coincidental? *Drug Safety* 2002; **25:** 929–42.

Effects on the neonate. For a suggestion that erythromycin or other macrolides might be associated with an increased risk of infantile hypertrophic pyloric stenosis in neonates, see under Effects on the Gastrointestinal Tract, above.

Effects on the skin. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have rarely been reported with macrolides.[1,2]

1. Lestico MR, Smith AD. Stevens-Johnson syndrome following erythromycin administration. *Am J Health-Syst Pharm* 1995; **52:** 1805–7.
2. Sullivan S, *et al.* Stevens-Johnson syndrome secondary to erythromycin. *Ann Pharmacother* 1999; **33:** 1369.

Overdosage. Acute pancreatitis was reported in a 12-year-old girl after ingestion of about 5 g of erythromycin base.[1] Transient pancreatitis has also been reported in another 15-year-old girl who took 5.328 g of erythromycin base.[2] Erythromycin produces contraction of the sphincter of Oddi resulting in reflux of bile into the pancreas but the resulting pancreatitis is self-limited and

remits when sphincter tone returns to normal after the erythromycin is eliminated from the body.

1. Berger TM, *et al.* Acute pancreatitis in a 12-year-old girl after an erythromycin overdose. *Pediatrics* 1992; **90:** 624–6.
2. Tenenbein MS, Tenenbein M. Acute pancreatitis due to erythromycin overdose. *Pediatr Emerg Care* 2005; **21:** 675–6.

Precautions

Erythromycin and its derivatives should be avoided in those known to be hypersensitive to it, or in those who have previously developed jaundice. All forms of erythromycin should be used with care in patients with existing liver disease or hepatic impairment, and the estolate is best avoided in such patients; liver function should be monitored. Repeated courses of the estolate or use for longer than 10 days increases the risk of hepatotoxicity.

The lactobionate should be used with caution in patients with severe renal impairment; dosage reduction may be necessary particularly in those who develop toxicity. A reduced dose of the estolate has also been recommended in severe renal impairment.

Erythromycin may aggravate muscle weakness in patients with myasthenia gravis.

Erythromycin should be used with care in patients with a history of arrhythmias or a predisposition to QT interval prolongation. Certain medications may also increase the risk of arrhythmias (see Interactions, below).

Erythromycin may interfere with some diagnostic tests including measurements of urinary catecholamines and 17-hydroxycorticosteroids. It has also been associated with falsely-elevated serum aspartate aminotransferase values when measured colorimetrically, although genuine elevations of this enzyme, due to hepatotoxicity, also occur, particularly with the estolate.

Erythromycin is irritant; solutions for parenteral use should be suitably diluted and given by intravenous infusion over 20 to 60 minutes to reduce the incidence of thrombophlebitis. Rapid infusion is also more likely to be associated with arrhythmias or hypotension.

Breast feeding. There has been a report[1] of a breast-fed infant who developed pyloric stenosis thought to be associated with use of erythromycin by the mother. A large Danish population-based cohort study[2] later concluded that the use of macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin, or spiramycin) during breast feeding increased the risk of infantile hypertrophic pyloric stenosis. (See also Effects on the Gastrointestinal Tract, above.) A milk-to-plasma ratio of 0.5 has been reported for erythromycin.[3] However, the American Academy of Pediatrics[4] states that, although erythromycin is concentrated in human breast milk, no adverse effects have been seen in breast-fed infants whose mothers were receiving erythromycin and it is therefore usually compatible with breast feeding.

1. Stang H. Pyloric stenosis associated with erythromycin ingested through breastmilk. *Minn Med* 1986; **69:** 669–70, 682.
2. Sørensen HT, *et al.* Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. *Scand J Infect Dis* 2003; **35:** 104–106.
3. Briggs GG, *et al. Drugs in pregnancy and lactation.* 7th ed. Philadelphia: Lippincott Williams and Wilkins, 2005.
4. 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 27/04/07)

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

Pregnancy. Of 298 pregnant women who took erythromycin estolate, clindamycin, or placebo for 3 weeks or longer, about 14, 4, and 3% respectively had abnormally high serum aspartate aminotransferase values.[1] Erythromycin estolate should probably not be given to pregnant women.

A study[2] of data from the Swedish Medical Birth Registry of infants born between July 1995 and December 2002 has examined details of infants exposed to erythromycin or phenoxymethylpenicillin during early pregnancy. Of 1844 exposed to erythromycin, 103 (5.6%) had congenital malformations compared with 420 of 9110 (4.7%) for phenoxymethylpenicillin. Of these, 34 (1.8%) and 86 (0.9%) respectively had a cardiovascular malformation, the rate being considered high for erythromycin. This contrasted with a previous study based on a 1980–96 dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities which found no signs of teratogenicity for erythromycin.[3] Although an increased risk for cardiovascular abnormalities was initially apparent when analysing erythromycin usage throughout pregnancy as reported by the mother, this was not confirmed when assessing usage only in the second or third month nor in the entire pregnancy for medically documented intake. The Swedish data also revealed a possible association between infant pyloric stenosis and early prenatal exposure to erythromycin[2] although others had previously failed to confirm such a risk[4] (see also Effects on the Gastrointestinal Tract, above).

1. McCormack WM, *et al.* Hepatotoxicity of erythromycin estolate during pregnancy. *Antimicrob Agents Chemother* 1977; **12:** 630–5.
2. Källén BAJ, *et al.* Is erythromycin therapy teratogenic in humans? *Reprod Toxicol* 2005; **20:** 209–14.
3. Czeizel AE, *et al.* A population-based case-control teratologic study of oral erythromycin treatment during pregnancy. *Reprod Toxicol* 1999; **13:** 531–6.
4. Hussain N, Herson VC. Erythromycin use during pregnancy in relation to pyloric stenosis. *Am J Obstet Gynecol* 2002; **187:** 821–2.

Interactions

Erythromycin and other macrolides have the potential to interact with a large number of drugs through their action on hepatic cytochrome P450 isoenzymes, particularly CYP1A2 and CYP3A4. Macrolides inhibit drug metabolism by microsomal cytochromes by competitive inhibition and by the formation of inactive complexes. Such interactions can result in severe adverse effects, including ventricular arrhythmias with astemizole, cisapride, and terfenadine. Enzyme inhibition is reported to be particularly pronounced with macrolides such as erythromycin and troleandomycin. Other macrolides such as azithromycin and dirithromycin are reported to have little or no effect on hepatic cytochromes, and consequently may produce fewer interactions (see also Mechanism, below).

Macrolides themselves have been reported rarely to prolong the QT interval and should be used with caution with other drugs known to also have this effect.

Other mechanisms by which macrolides cause interactions include suppression of the gastrointestinal flora responsible for the intraluminal metabolism of digoxin and possibly oral contraceptives, and the stimulant effect of macrolides on gastrointestinal motility which is believed to be responsible for the interaction between spiramycin and levodopa. An alternative mechanism by which macrolides increase serum concentrations of digoxin is thought to be via the inhibition of intestinal or renal P-glycoprotein transport of digoxin.

Few drugs are reported to affect erythromycin but cimetidine may increase and theophylline may decrease erythromycin concentrations (see below).

The effect on antimicrobial action when erythromycin is given with other antimicrobials is discussed under Antimicrobial Action, below.

◊ General references[1-4] to interactions associated with macrolide antibacterials.

1. von Rosenstiel N-A, Adam D. Macrolide antibacterials: drug interactions of clinical significance. *Drug Safety* 1995; **13:** 105–22.
2. Westphal JF. Macrolide-induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol* 2000; **50:** 285–95.
3. Pai MP, *et al.* Macrolide drug interactions: an update. *Ann Pharmacother* 2000; **34:** 495–513.
4. Shakeri-Nejad K, Stahlmann R. Drug interactions during therapy with three major groups of antimicrobial agents. *Expert Opin Pharmacother* 2006; **7:** 639–51.

Mechanism

In *rats* and humans, troleandomycin, and erythromycin and some of its derivatives, induce microsomal enzymes; the nitrosoalkane metabolites so formed produce stable inactive complexes with the iron of cytochrome P450. Eventually the oxidative metabolism of other drugs may be decreased. These effects are marked after troleandomycin, moderate after erythromycin, small after oleandomycin, and absent or negligible after josamycin, midecamycin, or spiramycin.[1,2]

1. Pessayre D, *et al.* Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother* 1985; **16** (suppl A): 181–94.
2. Periti P, *et al.* Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet* 1992; **23:** 106–31.

Drugs

For reference to the effects of erythromycin and other macrolides on other drugs, see

- alfentanil (p.17)
- bromocriptine (p.800)
- buspirone (p.966)
- carbamazepine (p.474)
- ciclosporin (p.1825)
- clozapine (p.984)
- colchicine (p.557)
- digoxin (p.1261)
- dihydroergotamine and ergotamine (p.621)
- disopyramide (p.1270)
- levodopa (p.807)
- midazolam and triazolam (p.989)
- phenytoin (p.498)
- pimozide (p.973)
- quetiapine (p.1023)
- quinidine (p.1384)
- repaglinide (p.458)
- rifabutin (p.324)
- sertraline (p.396)
- sildenafil (p.2194)
- simvastatin and other statins (p.1392)
- tacrolimus (p.1845)
- terfenadine (p.591)
- theophylline (p.1143)
- valproate (p.510)
- verapamil (p.1422)
- vinblastine (p.786)
- warfarin (p.1428)
- zopiclone (p.1039)

In the case of astemizole, cisapride, and terfenadine the UK CSM has warned that there is a risk of inducing ventricular arrhythmias if erythromycin, or possibly other macrolides, are also given,[1,2] and that, in particular, cisapride should not be used with macrolides.[3] The Commission on Human Medicines[4] (formerly CSM) later advised that amisulpride, ergotamine, dihydroergotamine, mizolastine, pimozide, simvastatin, and tolterodine should not be given with erythromycin. A warning was also issued that increased erythromycin concentrations may occur when used with other inhibitors of the cytochrome P450 CYP3A isoenzymes such as the azole antifungals, some calcium-channel blockers including diltiazem and verapamil, and HIV-protease inhibitors. For a report of an increased risk of sudden cardiac death associated with such combinations see Effects on the Cardiovascular System, above.

1. Committee on Safety of Medicines. Ventricular arrhythmias due to terfenadine and astemizole. *Current Problems 35* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024453&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
2. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid, Alimax): interactions with antifungals and antibiotics can lead to ventricular arrhythmias. *Current Problems* 1996; **22:** 1. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024458&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
3. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; **24:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 27/04/07)
4. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Erythromycin and other macrolides: focus on interactions. *Current Problems* 2006; **31:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/01/07)

Cimetidine. Cimetidine may increase plasma concentrations of erythromycin and deafness occurred in a patient taking both drugs.[1]

1. Mogford N, *et al.* Erythromycin deafness and cimetidine treatment. *BMJ* 1994; **309:** 1620.

Theophylline. Intravenous theophylline has been reported[1,2] to decrease serum concentrations of oral erythromycin although other studies[3,4] using intravenous or oral theophylline with intravenous erythromycin did not show any significant pharmacokinetic changes.

For reference to the effects of erythromycin on theophylline, see Macrolides, under Interactions of Theophylline, p.1143.

1. Iliopoulou A, *et al.* Pharmacokinetic interaction between theophylline and erythromycin. *Br J Clin Pharmacol* 1982; **14:** 495–9.
2. Paulsen O, *et al.* The interaction of erythromycin with theophylline. *Eur J Clin Pharmacol* 1987; **32:** 493–8.
3. Hildebrandt R, *et al.* Influence of theophylline on the renal clearance of erythromycin. *Int J Clin Pharmacol Ther Toxicol* 1987; **25:** 601–4.
4. Pasic J, *et al.* The interaction between chronic oral slow-release theophylline and single-dose intravenous erythromycin. *Xenobiotica* 1987; **17:** 493–7.

Antimicrobial Action

Erythromycin is a macrolide antibacterial with a broad and essentially bacteriostatic action against many Gram-positive and to a lesser extent some Gram-negative bacteria, as well as other organisms including some *Mycoplasma* spp., Chlamydiaceae, *Rickettsia* spp., and spirochaetes.

Mechanism of action. Erythromycin and other macrolides bind reversibly to the 50S subunit of the ribosome, resulting in blockage of the transpeptidation or translocation reactions, inhibition of protein synthesis, and hence inhibition of cell growth. Its action is mainly bacteriostatic, but high concentrations are slowly bactericidal against the more sensitive strains. Because macrolides penetrate readily into white blood cells and macrophages there has been some interest in their potential synergy with host defence mechanisms *in vivo*. The actions of erythromycin are increased at moderately alkaline pH (up to about 8.5), particularly in Gram-negative species, probably because of the improved cellular penetration of the nonionised form of the drug.

Spectrum of activity. Erythromycin has a broad spectrum of activity. The following pathogenic organisms are usually sensitive to erythromycin (but see also Resistance, below).

Gram-positive cocci, particularly streptococci such as *Streptococcus pneumoniae* and *Str. pyogenes* are sensitive. However, resistance has been increasingly reported in both organisms, particularly in penicillin-resistant *Str. pneumoniae*. Most strains of *Staphylococcus aureus* remain susceptible, although resistance can emerge rapidly, and some enterococcal strains are also susceptible.

Many other Gram-positive organisms respond to erythromycin, including *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Erysipelothrix rhusiopathiae*, and *Listeria monocytogenes*. Anaerobic *Clostridium* spp. are also usually susceptible, as is *Propionibacterium acnes*. *Nocardia* spp. vary in their susceptibility.

Gram-negative cocci including *Neisseria meningitidis* and *N. gonorrhoeae*, and *Moraxella catarrhalis* (*Branhamella catarrhalis*) are usually sensitive.

Other Gram-negative organisms vary in their susceptibility, but *Bordetella* spp., some *Brucella* strains, and *Flavobacterium* and *Legionella* spp. are usually susceptible. *Haemophilus ducreyi* is reportedly susceptible, but *H. influenzae* is somewhat less so. The Enterobacteriaceae are usually resistant, although some strains may respond at alkaline pH. *Helicobacter pylori* and most strains of *Campylobacter jejuni* are sensitive (about 1% of the latter are reported to be resistant in the USA).

Among the Gram-negative anaerobes most strains of *Bacteroides fragilis* and many *Fusobacterium* strains are resistant.

Other organisms usually sensitive to erythromycin include *Actinomyces*, Chlamydiaceae, rickettsias, spirochaetes such as *Treponema pallidum* and *Borrelia burgdorferi*, some mycoplasmas (notably *Mycoplasma pneumoniae*), and some of the opportunistic mycobacteria: *Mycobacterium scrofulaceum* and *M. kansasii* are usually susceptible, but *M. intracellulare* is often resistant and *M. fortuitum* usually so.

Fungi, yeasts, and viruses are not susceptible to erythromycin.

Activity with other antimicrobials. As with other bacteriostatic antimicrobials, the possibility of an antagonistic effect if erythromycin is given with a bactericide exists, and some antagonism has been shown *in vitro* between erythromycin and various penicillins and cephalosporins or gentamicin. However, in practice the results of such concurrent use are complex, and depend on the organism; in some cases synergy has been seen. For example, in the UK, the *BNF* recommends the use of amoxicillin with erythromycin or another macrolide such as azithromycin or clarithromycin for the treatment of uncomplicated community-acquired pneumonia if atypical organisms are suspected. Because of the adjacency of their binding sites on the ribosome, erythromycin may competitively inhibit the effects of chloramphenicol or lincosamides such as clindamycin or lincomycin.

Resistance. Several mechanisms of acquired resistance to erythromycin have been reported of which the most common is a plasmid-mediated ability to methylate ribosomal RNA, resulting in decreased binding of the antimicrobial drug. This can result in cross-resistance between erythromycin, other macrolides, lincosamides, and streptogramin B, because they share a common binding site on the ribosome and this pattern of resistance is referred to as the MLS_B phenotype. It is seen in staphylococci, and to a somewhat lesser extent in streptococci, as well as in a variety of other species including *B. fragilis*, *Clostridium perfringens*, *Corynebacterium diphtheriae*, and *Listeria* and *Legionella* spp.

Decreased binding of antimicrobial to the ribosome may also occur as a result of a chromosomal mutation, resulting in an alteration of the ribosomal proteins in the 50S subunit, which conveys one-step high-level erythromycin resistance. This form of resistance has been found in some strains of *Str. pneumoniae*, *H. pylori*, *M. pneumoniae*, *Escherichia coli*, *Str. pyogenes*, *Staph. aureus*, *and Campylobacter* spp.

Other forms of erythromycin resistance may be due to the production of a plasmid-determined erythromycin esterase that can inactivate the drug, or to decreased drug penetration. The latter may be partly responsible for the intrinsic resistance of Gram-negative bacteria like the Enterobacteriaceae, but has also been shown to be acquired as a plasmid-mediated determinant in some organisms; production of a protein which increases drug efflux from the cell is thought to explain the M phenotype resistance, in which organisms are resistant to 14-and 15-carbon ring macrolides, but retain sensitivity to 16-carbon ring macrolides, lincosamides, and streptogramins.

The incidence of resistance varies greatly with the area and the organism concerned and, although the emergence of resistance is rarely a problem in the short-term treatment of infection, it is quite common in conditions requiring prolonged treatment such as endocarditis due to *Staph. aureus*. The incidence of resistance in streptococci is generally lower than in *Staph. aureus* but shows geographical variation and may be increasing in some countries, including the UK. In addition, localised outbreaks of resistant strains may occur and produce a much higher incidence of resistance.

Antipseudomonal activity. Although macrolides have limited direct antibacterial activity against *Pseudomonas aeruginosa*, prolonged exposure at sub-MICs has produced antipseudomonal effects *in vitro*[1-3] and synergy has been shown with other antipseudomonals.[4] Erythromycin and clarithromycin appear to have the greatest activity. This action has been partly attributed to the ability of macrolides to reduce the protective biofilm produced by some strains of *P. aeruginosa*.[3,5] Other proposed mechanisms of action include modification of the inflammatory response to infection and direct inhibition of other virulence factors such as twitching motility.[3]

1. Tateda K, *et al*. Effects of sub-MICs of erythromycin and other macrolide antibiotics on serum sensitivity of Pseudomonas aeruginosa. *Antimicrob Agents Chemother* 1993; **37:** 675–80.
2. Tateda K, *et al*. Direct evidence of antipseudomonal activity of macrolides: exposure-dependent bactericidal activity and inhibition of protein synthesis by erythromycin, clarithromycin, and azithromycin. *Antimicrob Agents Chemother* 1996; **40:** 2271–5.
3. Wozniak DJ, Keyser R. Effects of subinhibitory concentrations of macrolide antibiotics on Pseudomonas aeruginosa. *Chest* 2004; **125** (suppl 2): 62S–69S.
4. Bui KQ, *et al*. In vitro and in vivo influence of adjunct clarithromycin on the treatment of mucoid Pseudomonas aeruginosa. *J Antimicrob Chemother* 2000; **45:** 57–62.
5. Yasuda H, *et al*. Interaction between biofilms formed by Pseudomonas aeruginosa and clarithromycin. *Antimicrob Agents Chemother* 1993; **37:** 1749–55.

Resistance. A meta-analysis[1] found that reported macrolide resistance in *Streptococcus pneumoniae* varied greatly from country to country. The percentage of erythromycin-resistant *Str. pneumoniae* in the USA (20.7%) was less than that in Europe (32.0%) although this difference was not considered statistically significant, and higher levels of resistance were found in Asia (57.3%). In Europe, *Str. pyogenes* showed greater resistance to erythromycin (36.8%) than *Str. pneumoniae*. However, across all regions, the mean resistance of *Str. pneumoniae* was statistically equivalent (30.4%) and also similar to that of *Str. pyogenes* (30.0%).

1. Halpern MT, *et al*. Meta-analysis of bacterial resistance to macrolides. *J Antimicrob Chemother* 2005; **55:** 748–57.

Pharmacokinetics

Erythromycin base is unstable in gastric acid, and absorption is therefore variable and unreliable. Consequently, the base is usually given in film- or enteric-coated preparations, or one of the more acid-stable salts or esters is used. Food may reduce absorption of the base or the stearate, although this depends to some extent on the formulation; the esters are generally more reliably and quickly absorbed and their absorption is little affected by food, so that the timing of doses in relation to food intake is unimportant.

Peak plasma concentrations generally occur between 1 and 4 hours after a dose and have been reported to range from about 0.3 to 1.0 micrograms/mL after 250 mg of erythromycin base, and from 0.3 to 1.9 micrograms/mL after 500 mg. Similar concentrations have been seen after equivalent doses of the stearate. Somewhat higher peak concentrations may be achieved on repeated use 4 times daily. Higher total concentrations are achieved after oral doses of the estolate or ethyl succinate, but only about 20 to 30% of estolate or 55% of ethyl succinate is present as the active base, the rest being present as the inactive ester (in the case of the estolate as the propionate). Peak concentrations of about 500 nanograms/mL of erythromycin base have been reported after 250 mg of the estolate or 500 mg of the ethyl succinate. A peak of 3 to 4 micrograms/mL can be achieved after 200 mg of gluceptate or lactobionate intravenously.

Erythromycin is widely distributed throughout body tissues and fluids, although it does not cross the blood-brain barrier well and concentrations in CSF are low. Relatively high concentrations are found in the liver and spleen, and some is taken up into polymorphonuclear lymphocytes and macrophages. Around 70 to 75% of the base is protein bound, but after doses as the estolate the propionate ester is stated to be about 95% protein bound. Erythromycin crosses the placenta: fetal plasma concentrations are variously stated to be 5 to 20% of those in the mother. It is distributed into breast milk.

Erythromycin is excreted in high concentrations in the bile and undergoes intestinal reabsorption. About 2 to 5% of an oral dose is excreted unchanged in the urine and as much as 12 to 15% of an intravenous dose may be excreted unchanged by the urinary route. Erythromycin is partly metabolised in the liver by the cytochrome P450 isoenzyme CYP3A4 via *N*-demethylation to inactive, unidentified metabolites. The half-life of erythromycin is usually reported to be about 1.5 to 2.5 hours, although this may be slightly longer in patients with renal impairment and has been reported to be between 4 to 7 hours in severe impairment.

Erythromycin is not removed by haemodialysis or peritoneal dialysis.

Uses and Administration

Erythromycin is a macrolide antibacterial with a wide spectrum of activity, that has been used in the treatment of a wide range of infections caused by susceptible organisms.

Its uses have included the treatment of severe campylobacter enteritis, chancroid, diphtheria, legionnaires' disease and other *Legionella* infections, neonatal conjunctivitis, pertussis, respiratory-tract infections including bronchitis, pneumonia (mycoplasmal and other atypical pneumonias as well as streptococcal), and sinusitis, and trench fever, and, combined with neomycin, for the prophylaxis of surgical infection in patients undergoing bowel surgery. It may be used as part of a multi-drug regimen for the treatment of inhalation and gastrointestinal anthrax. It is also used in the prevention of diphtheria in non-immune patients and of pertussis in non- or partially immune patients.

Erythromycin is used as an alternative to penicillin in penicillin-allergic patients with various conditions including actinomycosis, leptospirosis, listeriosis, mouth infections, otitis media (usually with a sulfonamide

such as sulfafurazole), pelvic inflammatory disease caused by *Neisseria gonorrhoeae*, pharyngitis, and staphylococcal and streptococcal skin infections. It has been used in the treatment of penicillin-allergic patients with syphilis, but there are doubts about its efficacy. It is also used in the prevention of perinatal or Group A streptococcal infections, rheumatic fever, and infections in splenectomised patients. In penicillin-allergic patients in the early stages of Lyme disease, erythromycin may be used as an alternative to a tetracycline; this use is generally restricted to pregnant women and young children, since it is less effective than other drugs. It is also used as an alternative to the tetracyclines in patients with cholera, *Chlamydia* or *Chlamydophila* infections (such as epididymitis, lymphogranuloma venereum, nongonococcal urethritis, pneumonia, psittacosis, and trachoma), Q fever, and spotted fevers.

For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Both oral and topical erythromycin may be used in acne (see Skin Disorders, below) and rosacea (p.1583).

Administration and dosage. Erythromycin may be given as the base or its salts or esters; doses are expressed in terms of the base. Each 1 g of erythromycin is equivalent to about the following amounts of each salt or ester:

- erythromycin estolate 1.44 g
- erythromycin ethyl succinate 1.17 g
- erythromycin gluceptate 1.31 g
- erythromycin lactobionate 1.49 g
- erythromycin propionate 1.08 g
- erythromycin stearate 1.39 g

The usual oral adult dose is the equivalent of erythromycin 1 to 2 g daily in 2 to 4 divided doses; for severe infections this may be increased to up to 4 g daily in divided doses. Daily doses higher than 1 g should be given in more than 2 divided doses.

For the prevention of streptococcal infections in patients with evidence of rheumatic fever or heart disease, who are unable to take penicillin or sulfonamides, a dose of 250 mg twice daily may be given.

For the management of acne, maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNF* recommends a dose of 500 mg twice daily.

In patients who are unable to take erythromycin orally and in those who are severely ill, in whom it is necessary to attain an immediate high blood concentration, erythromycin may be given intravenously as the lactobionate, in doses equivalent to those given orally. The gluceptate has also been used intravenously. To reduce the risk of venous irritation it should be given only by continuous or intermittent intravenous infusion of a solution containing not more than 0.5% of erythromycin. Intermittent infusions should be given every 6 hours over 20 to 60 minutes.

Doses may need to be limited in patients with renal impairment (see below).

For details of doses in children, including infants and adolescents, see below.

Other routes. Erythromycin was formerly given by intramuscular injection, but such injections are painful and are no longer generally recommended. Erythromycin is used as a 0.5% eye ointment for the treatment of superficial ocular infections, including neonatal conjunctivitis, caused by susceptible strains of bacteria and for the prophylaxis of neonatal conjunctivitis caused by *N. gonorrhoeae* or *C. trachomatis*. It may also be applied topically as a 2 to 4% gel or solution for the treatment of acne vulgaris and is also available in combination preparations with benzoyl peroxide, ichthammol, isotretinoin, tretinoin, and zinc acetate.

Propionyl erythromycin mercaptosuccinate has also been used. Erythromycin thiocyanate and erythromycin phosphate are used in veterinary medicine.

◊ Reviews.

1. Zhanel GG, *et al.* Review of macrolides and ketolides: focus on respiratory tract infections. *Drugs* 2001; **61:** 443–98.

Administration. A discussion of the significance of different formulations and salts used for oral preparations of erythromycin concluded that there was no clear evidence that any was superior in terms of clinical effect.[1]

1. Anonymous. Giving erythromycin by mouth. *Drug Ther Bull* 1995; **33:** 77–9.

Administration in children. The usual dose for infants and children is the equivalent of about 30 to 50 mg/kg of erythromycin daily in 2 to 4 divided doses although it may be doubled in severe infections. Based on age, the usual dose in children 2 to 8 years old is 1 g daily and in infants and children up to 2 years old 500 mg daily. Those over 8 years of age may be given the usual adult dose (see above).

For the prevention of streptococcal infections in children with evidence of rheumatic fever or heart disease, who are unable to take penicillin or sulfonamides, a dose of 250 mg twice daily may be given. The *BNFC* suggests a dose of 125 mg twice daily in those aged 1 month to 2 years. In addition, similar doses have been suggested for prophylaxis against pneumococcal infections.

For the management of acne, maintenance doses as low as 250 mg daily have been used but resistant strains of propionibacteria are widespread; the *BNFC* recommends a dose of 500 mg twice daily in those over 12 years of age. It also suggests a dose of 250 mg daily in 1 or 2 divided doses for infants with acne.

Although unlicensed in the UK for use in gastrointestinal stasis, the *BNFC* suggests a dose of 3 mg/kg given 4 times daily for infants and children up to 18 years of age (see also below).

Administration in renal impairment. A maximum dose of erythromycin 1.5 g daily has been suggested by the *BNF* for adult patients with severe renal impairment.

Decreased gastrointestinal motility. Erythromycin stimulates gut motility, apparently by acting as a motilin receptor agonist, although it has been suggested that it may have other actions as well.[1] It has been tried, with some success, for its prokinetic action in a small number of patients with decreased gastrointestinal motility (p.1694) including those with functional dyspepsia,[2] gastroparesis,[3] reflux ileus,[4] acute colonic pseudo-obstruction (Ogilvie's syndrome),[4,5] delayed gastric emptying after pancreatic-duodenal surgery,[6] and neonatal postoperative intestinal dysmotility.[7] It has also been used to increase gastrointestinal motility in critically ill, mechanically ventilated patients[8,9] and in preterm very low birth-weight infants.[10,11] However, the prophylactic or routine use of erythromycin in such circumstances has been cautioned against,[9,10] and a systematic review[12] of neonatal use also suggested that erythromycin should be reserved for a very small subset of high-risk preterm neonates with persistent or severe feed intolerance. Adverse effects associated with the long-term use of erythromycin that is necessary in, for example, diabetic gastroparesis, may also be problematic.[13]

For suggested doses in the treatment of children with gastrointestinal stasis, see Administration in Children, above.

1. Catnach SM, Fairclough PD. Erythromycin and the gut. *Gut* 1992; **33:** 397–401.
2. Arts J, *et al.* Influence of erythromycin on gastric emptying and meal related symptoms in functional dyspepsia with delayed gastric emptying. *Gut* 2005; **54:** 455–60.
3. Maganti K, *et al.* Oral erythromycin and symptomatic relief of gastroparesis: a systematic review. *Am J Gastroenterol* 2003; **98:** 259–63.
4. Armstrong DN, *et al.* Erythromycin for reflux ileus in Ogilvie's syndrome. *Lancet* 1991; **337:** 378.
5. Bonacini M, *et al.* Erythromycin as therapy for acute colonic pseudo-obstruction (Ogilvie's syndrome). *J Clin Gastroenterol* 1991; **13:** 475–6.
6. Yeo CJ, *et al.* Erythromycin accelerates gastric emptying after pancreaticoduodenectomy: a prospective, randomized, placebo-controlled trial. *Ann Surg* 1993; **218:** 229–38.
7. Simkiss DE, *et al.* Erythromycin in neonatal postoperative intestinal dysmotility. *Arch Dis Child* 1994; **71:** F128–9.
8. Chapman MJ, *et al.* Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. *Crit Care Med* 2000; **28:** 2334–7.
9. Hawkyard CV, Koerner RJ. The use of erythromycin as a gastrointestinal prokinetic agent in adult critical care: benefits versus risks. *J Antimicrob Chemother* 2007; **59:** 347–58.
10. Ng PC, *et al.* Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F177–F182.
11. Nuntnarumit P, *et al.* Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 2006; **148:** 600–605.
12. Patole S, *et al.* Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F301–F306.
13. Tanis AA, *et al.* Side-effects of oral erythromycin for treatment of diabetic gastroparesis. *Lancet* 1993; **342:** 1431.

Respiratory disorders. As well as their established antibacterial effect, it has been suggested that the 14-membered ring macrolides (such as clarithromycin, erythromycin, and roxithromycin) and the 15-membered ring macrolides (such as azithromycin) also have immunomodulatory and anti-inflammatory effects that could be useful in the management of respiratory diseases including asthma (p.1108), chronic obstructive pulmonary disease (p.1112), cystic fibrosis (p.166), diffuse panbronchiolitis, and sinusitis (p.193).[1-3] However, a systematic review[4] found insufficient evidence to support or refute the use of macrolides in chronic asthma although some clinical data indicated a positive effect; routine use was not recommended and further trials were warranted. A systematic review[5] on the use of macrolides in cystic fibrosis found evidence of a small but significant improvement in respiratory function at 6 months with azithromycin compared with placebo; the role of other macrolides was unclear and further studies were needed. A randomised, double-blind, placebo-controlled study[6] to evaluate the use of oral azithromycin given three times a week for 12 months for the treatment of cystic fibrosis in children, reported a significant reduction in the number of pulmonary exacerbations needing treatment with antibacterials, even in the absence of infection with *Pseudomonas aeruginosa*. Azithromycin has also been investigated[7-9] in the management of bronchiolitis obliterans in patients who have undergone lung transplantation (p.1815), although its role has yet to be defined.

1. Gotfried MH. Macrolides for the treatment of chronic sinusitis, asthma, and COPD. *Chest* 2004; **125** (suppl 2): 52S–61S.
2. Rubin BK, Henke MO. Immunomodulatory activity and effectiveness of macrolides in chronic airway disease. *Chest* 2004; **125** (suppl 2): 70S–78S.
3. Schultz MJ. Macrolide activities beyond their antimicrobial effects: macrolides in diffuse panbronchiolitis and cystic fibrosis. *J Antimicrob Chemother* 2004; **54:** 21–8.
4. Richeldi L, *et al.* Macrolides for chronic asthma. Available in the Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 02/03/07).
5. Southern KW, *et al.* Macrolide antibiotics for cystic fibrosis. Available in the Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 02/03/07).
6. Clement A, *et al.* Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 2006; **61:** 895–902.
7. Gottlieb J, *et al.* Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2008; **85:** 36–41.
8. Porhownik NR, *et al.* Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. *Can Respir J* 2008; **15:** 199–202.
9. Fietta AM, Meloni F. Lung transplantation: the role of azithromycin in the management of patients with bronchiolitis obliterans syndrome. *Curr Med Chem* 2008; **15:** 716–23.

Skin disorders. ***ACNE.*** Erythromycin may be used topically or orally in the treatment of acne (p.1577). Topical erythromycin may be used for mild inflammatory acne if benzoyl peroxide is ineffective or poorly tolerated. It is also used as adjunctive treatment in more severe acne. Erythromycin is also available as a complex with zinc acetate that has been reported to be more effective than topical erythromycin alone[1] or oral minocycline.[2] However, development of antibiotic resistance by the skin flora is an increasing problem. Combination therapy with benzoyl peroxide and erythromycin has been reported to be helpful in preventing the selection of antibiotic-resistant mutants[3,4] and to be more effective than topical clindamycin alone.[5] Alternatively, short intervening courses of benzoyl peroxide during antibacterial therapy may help to eliminate any resistant bacteria that have been selected.[6] It has also been recommended that courses of topical antibiotics be continued for no longer than necessary (although treatment should be used for at least 6 months), that the same drug be used if further treatment is required, and that treatment with different oral and topical antibiotics or antibiotic rotation be avoided.[6]

Oral erythromycin may be used as an alternative to a tetracycline in moderate acne. However, resistance to erythromycin is increasing so it may be best reserved for those patients in whom other antibacterials are unsuitable.

1. Habbema L, *et al.* A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. *Br J Dermatol* 1989; **121:** 497–502.
2. Stainforth J, *et al.* A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris. *J Dermatol Treat* 1993; **4:** 119–22.
3. Eady EA, *et al.* Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br J Dermatol* 1994; **131:** 331–6.
4. Eady EA, *et al.* The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol* 1996; **134:** 107–13.
5. Packman AM, *et al.* Treatment of acne vulgaris: combination of 3% erythromycin and 5% benzoyl peroxide in a gel compared to clindamycin phosphate lotion. *Int J Dermatol* 1996; **35:** 209–11.
6. Eady EA, *et al.* Antibiotic resistant propionibacteria in acne: need for policies to modify antibiotic usage. *BMJ* 1993; **306:** 555–6.

Preparations

BP 2008: Erythromycin and Zinc Acetate Lotion; Erythromycin Estolate Capsules; Erythromycin Ethyl Succinate Oral Suspension; Erythromycin Ethyl Succinate Tablets; Erythromycin Lactobionate Intravenous Infusion; Erythromycin Stearate Tablets; Gastro-resistant Erythromycin Tablets;
USP 31: Erythromycin and Benzoyl Peroxide Topical Gel; Erythromycin Delayed-release Capsules; Erythromycin Delayed-release Tablets; Erythromycin Estolate and Sulfisoxazole Acetyl Oral Suspension; Erythromycin Estolate Capsules; Erythromycin Estolate for Oral Suspension; Erythromycin Estolate Oral Suspension; Erythromycin Estolate Tablets; Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension; Erythromycin Ethylsuccinate for Oral Suspension; Erythromycin Ethylsuccinate Injection; Erythromycin Ethylsuccinate Oral Suspension; Erythromycin Ethylsuccinate Tablets; Erythromycin Lactobionate for Injection; Erythromycin Ointment; Erythromycin Ophthalmic Ointment; Erythromycin Pledgets; Erythromycin Stearate Tablets; Erythromycin Tablets; Erythromycin Topical Gel; Erythro-

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.

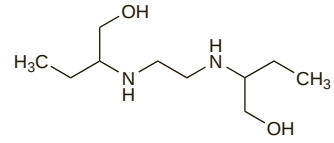
Этамбутола Гидрохлорид

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