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