

PRODUCT INFORMATION

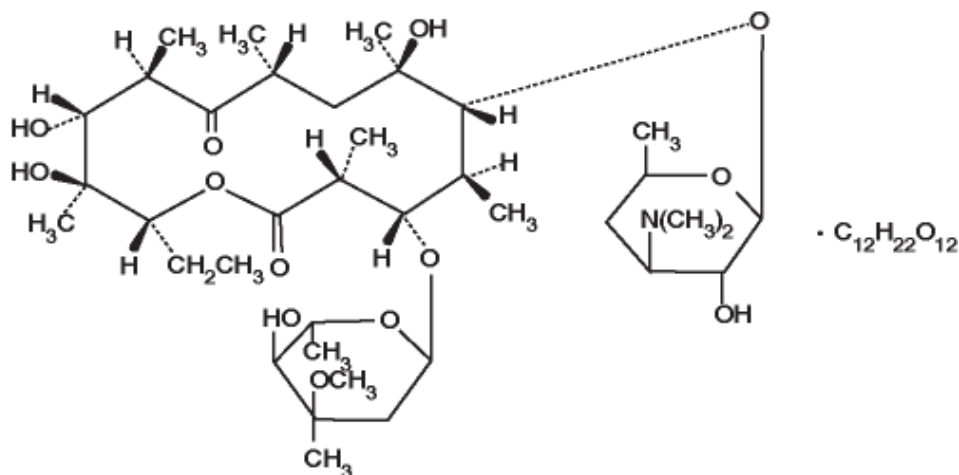
ERYTHROCIN IV erythromycin 1g (as lactobionate) powder for injection vial

NAME OF THE MEDICINE

Erythromycin Lactobionate

Erythromycin lactobionate is chemically known as erythromycin mono (4-O-beta-D-galactopyranosyl-D-gluconate) (salt). Its molecular formula is $C_{37}H_{67}NO_{13} \cdot C_{12}H_{22}O_{12}$ and the molecular weight is 1092.23.

The structural formula is:



CAS Number: 3847-29-8

DESCRIPTION

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids.

Erythrocin IV (sterile erythromycin lactobionate) is a soluble salt of erythromycin suitable for intravenous administration. It is available as a sterile, lyophilized cake for reconstitution containing the equivalent of 1 g erythromycin activity.

PHARMACOLOGY

Intravenous infusion of 500 mg of erythromycin lactobionate at a constant rate over 1 hour in fasting adults produced a mean serum erythromycin level of approximately 7 microgram/mL at 20 minutes, 10 microgram/mL at 1 hour, 2.6 microgram/mL at 2.5 hours and 1 microgram/mL at 6 hours.

The extent of plasma protein binding has been variably reported but is probably of the order of 75%. Erythromycin diffuses readily into most body fluids with the exception of cerebrospinal fluid, synovial fluid and vitreous humor. In the presence of normal renal function, the plasma half life is approximately 1.4 hours; this may increase to 6 hours in anuric patients but does not usually require dosage adjustment. Erythromycin is not removed by dialysis.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile. However, only a small proportion of the administered dose appears in the bile. The effect of hepatic dysfunction on biliary excretion of erythromycin is not known. Approximately 12 to 15 percent of an intravenously administered dose of erythromycin is excreted in the urine unchanged. A substantial proportion of the administered dose remains unaccounted for and is presumably metabolised probably in the liver.

Erythromycin appears in breast milk at levels which are approximately 50% of the plasma concentration. It crosses the placenta and foetal plasma levels are usually 5%-20% of the maternal plasma concentration.

Microbiology

Erythromycin binds to the 50S ribosomal subunits of susceptible bacteria and suppresses protein synthesis. The mode of action of erythromycin is by inhibition of the protein synthesis without affecting nucleic acid synthesis.

Erythromycin is usually active *in vitro* against the following Gram positive and Gram negative organisms.

Streptococcus pyogenes
Alpha-haemolytic streptococcus (viridans group)
Staphylococcus aureus
Streptococcus pneumoniae
Corynebacterium diphtheriae (as an adjunct to antitoxin)
Corynebacterium minutissimum
Listeria monocytogenes
Clostridium tetani
Neisseria gonorrhoeae
Bordetella pertussis
Haemophilus influenzae (some strains are resistant)
Legionella pneumophila
Treponema pallidum
Chlamydia trachomatis
Mycoplasma pneumoniae
Campylobacter jejuni (in severe or prolonged cases)
Ureaplasma urealyticum

Not all strains of the organism listed above are sensitive and culture and susceptibility testing should be done. Several strains of *Haemophilus influenzae* and staphylococci have been found to be resistant to erythromycin. Staphylococci resistant to erythromycin may emerge during a course of therapy. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin and chloramphenicol.

Susceptibility Testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regular updated, recognized and standardised method (eg.CLSI).

Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

- A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

- A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation.

- A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable: other therapy should be selected.

Note 1: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Note 2: Many strains of *Haemophilus influenzae* are resistant to erythromycin alone, but are susceptible to erythromycin and sulfonamides together. Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Culture and susceptibility testing should be performed.

INDICATIONS

Oral erythromycin is not considered to be the antibiotic of choice in severely ill patients.

- Erythrocin IV (sterile erythromycin lactobionate) is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below when oral administration is not possible or when the severity of the infection requires immediate high serum levels of erythromycin. Intravenous therapy should be replaced by oral administration at the appropriate time.
- Upper respiratory tract infections caused by *Streptococcus pyogenes* (Group A beta-haemolytic streptococci); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); *Haemophilus influenzae* (many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved).

- Lower respiratory tract infections caused by *Streptococcus pyogenes* (Group A beta-haemolytic streptococci); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*).
- Respiratory tract infections due to *Mycoplasma pneumoniae*.
- Skin and skin structure infections caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).
- Diphtheria - As an adjunct to diphtheria antitoxin in infections due to *Corynebacterium diphtheriae* to prevent establishment of carriers and to eradicate the organism in carriers.
- Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythrocin IV (sterile erythromycin lactobionate) followed by erythromycin stearate, base or ethyl succinate orally, as an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin.
- Before treatment of gonorrhoea, patients who are suspected of also having syphilis should have microscopic examination for *T. pallidum* (by immuno-fluorescence or dark field) before receiving erythromycin and monthly serologic tests for a minimum of 4 months thereafter.
- Legionnaires' Disease caused by *Legionella pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

CONTRAINDICATIONS

- Erythromycin is contraindicated in patients with known hypersensitivity to erythromycin or any of excipients in the formulation, or to other antibiotics from the macrolide family.
- Severely impaired hepatic function.
- Concurrent treatment with terfenadine, astemizole, cisapride, pimozide, ergotamine or dihydroergotamine is contraindicated. (See **PRECAUTIONS - Interactions with other Medicines**)

PRECAUTIONS

Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), have been reported with the intravenous administration of erythromycin. Limited data suggest that these adverse effects may be associated with abnormally elevated serum erythromycin concentrations following rapid administration. Erythromycin therefore must not be administered rapidly by direct intravenous injection (IV push) (see **DOSAGE AND ADMINISTRATION**).

There have been reports of hepatic dysfunction, including increased liver enzymes and hepatocellular and/or cholestatic hepatitis with or without jaundice occurring in patients receiving erythromycin products.

The use of erythromycin can lead to the development of severe colitis as a result of colonisation with *C. difficile*, a toxin-producing organism. The colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can be fatal. If significant diarrhoea occurs (this may, however, begin up to several weeks after cessation of antibiotic therapy) erythromycin should be discontinued. This may be sufficient treatment in the early stages although cholestyramine orally may help by binding the toxin in the colonic lumen. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Treatment with bacitracin has also been reported to be successful. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil), may prolong and/or worsen the condition and should not be used. Vancomycin is not effective if given parenterally. Fluids, electrolytes and protein replacement therapy should be provided when indicated.

There have been reports suggesting erythromycin does not reach the foetus in adequate concentration to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regime.

Since Erythromycin is principally excreted by the liver caution should be exercised when erythromycin is administered to patients with impaired hepatic function.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See **Interactions with other Medicines**)
Erythromycin may aggravate the weakness of patients with myasthenia gravis.

Overgrowth of non-susceptible bacteria or fungi may occur during prolonged or repeated therapy.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

Effects on the Neonate

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents should be informed to contact their physician if vomiting or irritability with feeding occurs.

Effects on Fertility

There was no apparent effect on male or female fertility in rats treated with erythromycin base by oral gavage at 700 mg/kg/day (approximately 9 times the human dose).

Use in Pregnancy (Category A)

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

No evidence of teratogenicity or embryotoxicity was observed when erythromycin base was given by oral gavage to pregnant rats and mice at 700 mg/kg/day (approximately 9 times the maximum human dose), and to pregnant rabbits at 125 mg/kg/day (approximately 1.5 times the maximum human dose).

A slight reduction in birth weights was noted when female rats were treated prior to mating, during mating, gestation and lactation at an oral dosage of 700 mg/kg/day of erythromycin base; weights of the offspring were comparable to those of the controls by weaning. No evidence of teratogenicity or effects on reproduction was noted at this dosage. When administered during late gestation and lactation periods, this dosage of 700 mg/kg/day (14 times the maximum human dose) did not result in any adverse effects on birth weight, growth and survival of offspring.

There are no adequate and well-controlled studies in pregnant women. However, observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.

Erythromycin has been reported to cross the placental barrier in humans, but fetal plasma levels are generally low.

Erythromycin should be used by women during pregnancy only if clearly needed.

Use in Lactation

Erythromycin is excreted in breast milk. Caution should be exercised when erythromycin is administered to a nursing woman.

Paediatric Use

See "INDICATIONS " and "DOSAGE AND ADMINISTRATION" sections.

Carcinogenicity

Long-term (2 year) oral studies conducted in rats up to about 400 mg/kg/day and in mice up to about 500 mg/kg/day with erythromycin stearate did not provide evidence of tumourigenicity.

Genotoxicity

Erythromycin was not genotoxic in assays for bacterial and mammalian mutagenicity and for clastogenicity *in vitro*. The clastogenic potential of erythromycin has not been investigated *in vivo*.

Interactions with other Medicines

There have been reports that there is a rise in plasma levels of cyclosporin, phenytoin, hexobarbital, alfentanil, carbamazepine, quinidine, disopyramide, bromocriptine, methylprednisolone, vinblastine, sildenafil, cilostazol, valproate, tacrolimus, terfenadine, astemizole, rifabutin, verapamil and diltiazem (drugs metabolized by the cytochrome P450 system) during concomitant administration of erythromycin.

Theophylline:

Recent data from studies of erythromycin reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

There have been published reports suggesting that when oral erythromycin is given concurrently with theophylline there is a significant decrease in erythromycin serum concentrations. This decrease could result in subtherapeutic concentrations of erythromycin.

Carbamazepine:

Erythromycin administration in patients receiving carbamazepine has been reported to cause increased serum levels of carbamazepine with subsequent development of signs of carbamazepine toxicity.

Digoxin:

Concomitant administration of erythromycin and digoxin has been reported to result in elevated serum digoxin levels.

Oral anticoagulants:

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly.

Triazolam and midazolam:

Triazolam and midazolam plasma concentrations may approximately double when erythromycin is co-administered, due to a reduction in clearance and increase in elimination half-life but drug accumulation has not been observed with repeated dosing. Therefore consideration of dose reduction may be appropriate in patients treated concurrently with triazolam or midazolam and erythromycin.

Colchicine:

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine.

Astemizole:

Erythromycin significantly alters the metabolism of astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events including cardiac arrest, torsade de pointes and other ventricular arrhythmias have been observed (see **CONTRAINDICATIONS** and **ADVERSE EFFECTS**).

Terfenadine

Erythromycin significantly alters the metabolism of terfenadine when taken concomitantly. Rare cases of serious cardiovascular adverse events including death, cardiac arrest, torsade de pointes and other ventricular arrhythmias have been observed (see **CONTRAINDICATIONS** and **ADVERSE EFFECTS**).

Cisapride

Elevated cisapride levels have been reported in patients receiving erythromycin, and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed in patients taking pimozide and clarithromycin, another macrolide antibiotic,

Ergotamine/dihydroergotamine:

Post-marketing reports indicate that co-administration of erythromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the central nervous system. (See **CONTRAINDICATIONS**)

Zopiclone:

Erythromycin has been reported to decrease the clearance of zopiclone and thus may increase the pharmacodynamic effects of this drug.

HMG-CoA Reductase Inhibitors:

Erythromycin has been reported to increase concentrations of HMG-CoA Reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Interactions with Laboratory Tests

Erythromycin interferes with the fluorimetric determination of urinary catecholamines.

ADVERSE EFFECTS

Side effects following the use of intravenous erythromycin are rare. Occasional venous irritation has been encountered, but if the infusion is given slowly, in dilute solution, preferably by continuous intravenous infusion or intermittent infusion in no less than 60 minutes, pain and vessel trauma are minimized.

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin products. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur.

Pseudomembranous colitis has been rarely reported in association with erythromycin therapy.

Occasional vomiting, abdominal cramping and abdominal pain have been reported.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have rarely been reported.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), have been reported less commonly with the intravenous administration of erythromycin. Limited data suggest that these adverse effects may be associated with abnormally elevated serum erythromycin concentrations following rapid administration. There have been isolated reports of other cardiovascular symptoms such as chest pain, dizziness and palpitations; however a cause and effect relationship has not been established.

Central nervous system side effects, including seizures, hallucinations, confusion vertigo and tinnitus have been reported in occasional patients; however, a cause and effect relationship has not been established.

There have been rare reports of pancreatitis and convulsions.

There have been reports of interstitial nephritis coincident with erythromycin use.

Infantile Hypertrophic Pyloric Stenosis (IHPS):

7 out of 157 [5%] newborns developed severe non-bilious vomiting or irritability with feeding and IHPS who were given oral erythromycin for pertussis prophylaxis. The relative risk of IHPS was increased 6.8 fold (95% CI=3-16) compared to a retrospective cohort of infants.

DOSAGE AND ADMINISTRATION

Note: For I.V. administration only

Do not administer as a bolus. Erythrocin IV (sterile erythromycin lactobionate) must be administered by continuous or intermittent intravenous infusion only. Due to the local irritative effects of erythromycin as well as reports of QT interval prolongation and ventricular arrhythmias (some of which have been fatal) being associated with elevated serum concentrations of erythromycin, the drug must not be administered rapidly by direct intravenous injection (IV push).

Continuous infusion of erythromycin lactobionate is preferable due to the slower infusion rate and its lower concentration of erythromycin; however, intermittent infusion at six hour intervals is also effective. Intravenous erythromycin should be replaced by oral erythromycin as soon as possible.

For slow continuous infusion: The final diluted solution of erythromycin lactobionate is prepared to give a concentration of 1 g per litre (1 mg/mL).

For intermittent infusion: Administer one-fourth the total daily dose of erythromycin lactobionate by intravenous infusion over a minimum of 60 minutes at intervals not greater than every six hours. A longer period of infusion should be used in patients with risk factors or previous evidence of arrhythmias. The final diluted solution of erythromycin lactobionate is prepared to give a concentration of 1 to 5 mg/mL. No less than 100 mL of intravenous diluent should be used. Infusion should be sufficiently slow to minimize pain along the vein.

For the treatment of severe infections in adults and children, the recommended intravenous dose of erythromycin lactobionate is 15 to 20 mg/kg/day. Higher doses, up to 4 g/day, may be given for severe infections.

For treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae*, in female patients hypersensitive to penicillins, administer 500 mg erythromycin lactobionate every six hours for three days, followed by oral administration of 250 mg erythromycin stearate or base, or 400mg erythromycin ethyl succinate, every six hours for seven days.

For treatment of Legionnaires' Disease: Although optimal doses have not been established, doses utilized in reported clinical data were 1 to 4 grams daily in divided doses.

Preparation of solution:

1. Prepare the initial solution of Erythrocin IV by adding 20 ml of sterile water for injection to the 1 g vial. Use only Sterile Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. Ensure that the contents of the vial are fully dissolved before using the product. The volume after reconstitution contains an excess to ensure that the stated volume can be withdrawn.

After reconstitution, each mL contains 50 mg of erythromycin activity.

2. Add the initial dilution to one of the following diluents before administration to give a concentration of 1 g of erythromycin activity per litre (1 mg/mL) for continuous infusion or 1 to 5 mg/mL for intermittent infusion:

0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Normosol-r[®].

3. The following solutions may also be used providing they are first buffered with 8.4% Sodium Bicarbonate Solution (add 0.5mL of 8.4% Sodium Bicarbonate Solution per 100 mL of solution):

5% glucose injection

5% glucose and Lactated Ringer's Injection.

5% glucose and 0.9% Sodium Chloride Injection

Note: 8.4% Sodium Bicarbonate Solution must be added to these solutions so that their pH is in the optimum range for erythromycin lactobionate stability. Acidic solutions of erythromycin lactobionate are unstable and lose their potency rapidly. A pH of at least 5.5 is desirable for the final diluted solution of erythromycin lactobionate.

No drug or chemical agent should be added to an erythromycin lactobionate IV fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

Stability:

To reduce the microbiological hazard, use as soon as practicable after reconstitution. The final diluted solution of erythromycin lactobionate should be completely administered within 8 hours, since it is not suitable for storage. If storage is necessary, hold at 2-8°C for not more than 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

OVERDOSAGE

Reports indicate that the ingestion of large amounts of erythromycin can be expected to produce gastrointestinal distress, hearing problems and other Adverse Effects (see **ADVERSE EFFECTS**). Allergic reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures. Erythromycin serum levels are not appreciably altered by haemodialysis or peritoneal dialysis.

For advice on the management of overdose please contact the Poisons Information Centre. In Australia please call 13 11 26 and in New Zealand 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Erythrocin IV (erythromycin lactobionate), powder for injection is supplied as a sterile, lyophilized cake for reconstitution in single vials, containing the equivalent of 1 g of erythromycin.

Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE - S4

Date of approval

Date of TGA Approval

08 January 2008

Date of most recent amendment

23 June 2008

Version 01