PRODUCT INFORMATION

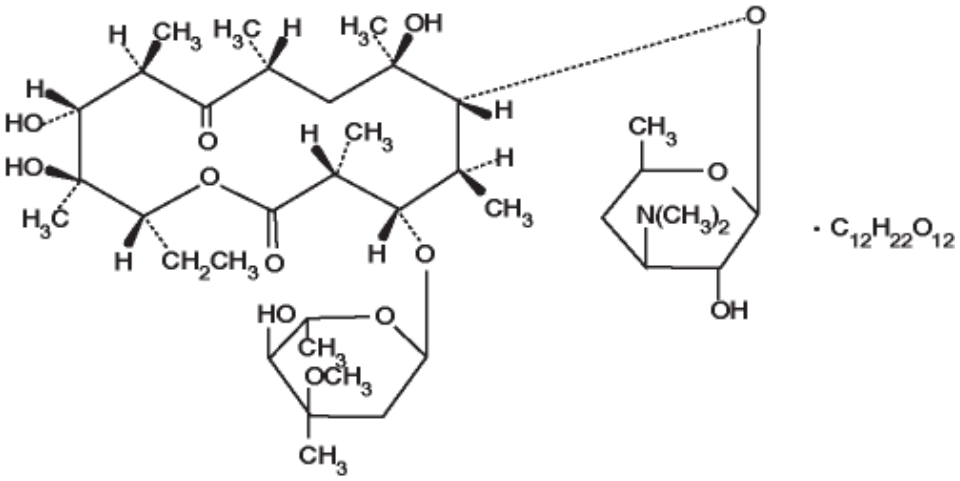
ERYTHROCIN® IV erythromycin (as lactobionate) powder for injection

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 $C_{37}H_{67}NO_{13}•C_{12}H_{22}O_{12}$ and the molecular weight is 1092.23.

Structural formula:



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

Pharmacokinetics

Absorption

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.

Distribution

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.

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 (see **PRECAUTIONS**).

Elimination

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.

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.

Susceptibility testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regular updated, recognised and standardised method (e.g. 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 the case of:

- Hypersensitivity to erythromycin or any of excipients in the formulation (see **DESCRIPTION**)
- Hypersensitivity to other antibiotics from the macrolide family
- Severely impaired hepatic function
- Concurrent treatment with HMG-CoA reductase inhibitors (e.g. lovastatin or simvastatin), ergotamine or dihydroergotamine (see **INTERACTIONS WITH OTHER MEDICINES**)
- Congenital or acquired QT interval prolongation
- Clinically relevant cardiac arrhythmias (e.g. ventricular arrhythmias) or in severe congestive heart failure (NYHA IV)
- Concomitant intake of medicinal products, which can lead to prolongation of the QT interval and under some circumstances to life-threatening ventricular arrhythmia (torsade de pointes) e.g. terfenadine, astemizole, cisapride, pimozide, domperidone, class IA and III antiarrhythmics (e.g. disopyramide), certain neuroleptics, tri- and tetracyclic antidepressants, arsenic trioxide, methadone, budipine, certain fluoroquinolones, imidazole anti-mycotics and anti-malarials (e.g. pentamidin i.v.) (see **INTERACTIONS WITH OTHER MEDICINES**)
- Disturbances of the electrolyte balance (especially in the case of hypokalaemia and hypomagnesaemia)
- Rapid administration by direct intravenous injection (IV push) (see **PRECAUTIONS**).

PRECAUTIONS

<u>QT prolongation</u>

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**). Erythromycin is contraindicated in patients with high risk factors for cardiac arrhythmia (see **CONTRAINDICATIONS**). Elderly patients may be more susceptible to drug-associated effects on the QT interval.

If during therapy with erythromycin symptoms such as palpitations, dizziness or syncope occur which can be signs of arrhythmia, an investigation of the patient including Electrocardiogram and determination of the QT interval should be initiated immediately.

Electrolyte disturbances promote the probability of cardiac arrhythmia. In the case of risk factors for electrolyte disturbances (such as diuretic/laxative medication, vomiting, diarrhoea, use of insulin in emergency situations, renal diseases or anorectic conditions), adequate laboratory tests and if necessary an adequate electrolyte balance should be carried out.

Patients with impaired hepatic function/liver damage

There have been reports of hepatic dysfunction, including increased liver enzymes, hepatomegaly and hepatocellular and/or cholestatic hepatitis with or without jaundice in patients receiving erythromycin products (see **ADVERSE EFFECTS)**. Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. Erythromycin is contraindicated in severe hepatic impairment (see **CONTRAINDICATIONS**).

Patients with existing liver damage and allergies may be at higher risk of intrahepatic cholestasis and cholestatic jaundice due to sensitisation, resulting in colicky abdominal pain, nausea, vomiting, urticaria, eosinophilia and fever. Although these reactions can occur after initial administration, the risk increases with repeated administration and therapy lasting longer than 10 days (see **ADVERSE EFFECTS**).

Clostridium difficile-associated diseases

The use of erythromycin can lead to the development of severe colitis as a result of colonisation with *C. difficile*, a toxin-producing organism. Colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can range in severity from mild diarrhoea to fatal colitis. If significant diarrhoea occurs, erythromycin should be discontinued (diarrhoea however, may begin several weeks to over two months after cessation of antibiotic therapy). 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.

Medicines 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.

Musculature and nervous system

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with simvastatin, lovastatin or atorvastatin (see **INTERACTIONS WITH OTHER MEDICINES)**. The concomitant use of these medicines with erythromycin is contraindicated (see **CONTRAINDICATIONS**).

Concomitant use of erythromycin with other statins should be instructed by the physician to pay attention to signs of myopathy (e.g. inexplicable muscle pain or weakness or dark coloured urine). If myopathy occurs, the intake of the statin has to be stopped immediately.

Erythromycin may aggravate the weakness of patients with myasthenia gravis.

Allergic reactions

With the administration of erythromycin, severe, life-threatening allergic reactions may occur, e.g. severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis (especially in children of all ages), as well as angioneurotic oedema or anaphylaxis. A cross allergy in patients with hypersensitivity to macrolide antibiotics can exist, so in patients with known hypersensitivity to macrolides or related substances (e.g. ketolides), special caution is recommended. At first signs of hypersensitivity, erythromycin has to be stopped immediately and necessary symptomatic emergency measures initiated.

Prolonged or repeated therapy

Overgrowth of non-susceptible bacteria or fungi may occur during prolonged or repeated therapy. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

In the case of a treatment duration longer than 3 weeks, it is recommended that whole blood count and hepatic and renal function tests be performed at regular intervals.

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

Eye disorder

There is a risk for developing visual impairments after exposure to erythromycin. For some patients, a pre-existing dysfunction in mitochondrial metabolism from genetic causes such as Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) might play a contributing role.

Pneumonia

Due to very common resistance of *Streptococcus pneumoniae* against macrolides, erythromycin is not the first-choice therapy in case of ambulant acquired pneumonia. In hospital acquired pneumonia, erythromycin should only be used in combination with other antibiotics.

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)

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 foetal plasma levels are generally low. 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 regimen.

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

Use in lactation

Erythromycin is concentrated in breast milk and adverse effects have been seen in breast-fed infants including gastrointestinal disturbances, pyloric stenosis (see **Paediatric use**), sensitisation or colonisation with fungi. Caution should be exercised when erythromycin is administered to a nursing woman.

Paediatric use

To avoid liver damage due to overdose in infants and toddlers, dosing should be dependent on the clinical picture and the course of the disease.

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.

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.*

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.

Effect on laboratory tests

Erythromycin interferes with the fluorimetric determination of urinary catecholamines.

Effect on ability to drive and use machines

Erythromycin has a negligible influence on the ability to concentrate and react. However, the occurrence of undesirable effects can negatively influence the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

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 (e.g. warfarin) were used concomitantly.

Medicines that prolong the QTc interval

Erythromycin has been shown to prolong the QTc interval and is associated with case reports of torsade de pointes in some patients. Patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving medicines that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmics, certain neuroleptics, tri- and tetracyclic antidepressants, ebastine, arsenic trioxide, methadone, budipine, certain fluoroquinolones, imidazole antimycotics and anti-malarials (e.g. pentamidin i.v.), are at increased risk of ventricular arrhythmias. As these predisposing conditions may increase the risk for ventricular arrhythmias, erythromycin should not be used in patients with ongoing proarrhythmic conditions (see **CONTRAINDICATIONS)**.

Medicines metabolised by the cytochrome P450 system

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome P450 system (CYP3A) and P-glycoprotein. Co-administration of erythromycin and a medicine primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic or adverse effects of the concomitant medicine e.g. ciclosporin, phenytoin, felodipine, hexobarbital, carbamazepine, alfentanil, quinidine, disopyramide, bromocriptine, methylprednisolone, vinblastine, sildenafil, cilostazol, valproate, tacrolimus, terfenadine, mizolastine, domperidone, astemizole, rifabutin, verapamil, diltiazem, acenocoumarol, digoxin, dihydroergotamine, ergotamine, midazolam, omeprazole, theophylline, triazolam and antifungals (e.g. fluconazole, ketoconazole and itraconazole). Dosage adjustments

may be considered, and when possible, serum concentrations of medicines primarily metabolised by CYP3A4 should be monitored closely in patients receiving erythromycin.

Erythromycin has been shown to prolong the QTc interval and is associated with case reports of torsades de pointes in some patients. In one published study patients who used both oral erythromycin and strong CYP3A inhibitors (azole antifungal medicines [ketoconazole, itraconazole and fluconazole, all administered systemically], diltiazem, verapamil, troleandomycin, mibefradil, nefazodone) had a risk of sudden death from cardiac causes that was five times as great as that among patients who had not used these medicines. Many of the medicines that are known to block CYP3A4 also have direct effects on repolarisation, which may cause a dramatic lengthening of the QT interval. Given that there are alternatives to erythromycin and these listed CYP3A inhibitors, the use of these combinations should be avoided.

Hypotension, bradyarrhythmia and lactic acidosis have been observed in patients receiving concurrent verapamil.

Medicines that induce CYP3A (such as rifampicin, phenytoin, carbamazepine, phenobarbital (phenobarbitone), St John's Wort) may induce the metabolism of erythromycin. This may lead to sub-therapeutic levels of erythromycin and a decreased effect. The induction decreases gradually after discontinuing treatment with CYP3A4 inducers. Erythromycin should not be used during, or for two weeks after stopping treatment, with CYP3A4 inducers.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other medicines metabolised by the CYP3A isoform are also possible. The following CYP3A based drug interactions have been observed with erythromycin products in post-marketing experience:

Triazolobenzodiazepines (triazolam, alprazolam and midazolam)

Triazolam, alprazolam 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, alprazolam or midazolam and erythromycin.

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**).

Sildenafil

Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered.

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 medicines concomitantly (see **CONTRAINDICATIONS**).

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

Astemizole & terfenadine
Erythromycin significantly alters the metabolism of astemizole & terfenadine 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**).

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 (see **CONTRAINDICATIONS**).

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

Anti-bacterial agents
Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin and chloramphenicol. Same interaction is applicable with streptomycin, tetracyclines, colistin and bactericidal beta-lactam antibiotics (e.g. penicillin, cephalosporin).

Cimetidine
It may inhibit the metabolism of erythromycin which may lead to an increased plasma concentration.

Protease inhibitors
Protease inhibitors (e.g. ritonavir) has been reported to increase the level of effect of erythromycin by altering drug metabolism.

ADVERSE EFFECTS

Adverse 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 minimised.

The following adverse effects have been reported for erythromycin. The adverse effects are listed according to the frequency defined as:

Very common (≥ 1/10)
Common (≥ 1/100 - < 1/10)
Uncommon (≥ 1/1000 - < 1/100)
Rare (> 1/10000 - < 1/1000)
Very rare (< 1/10000)
Not known (cannot be estimated from the available data)

Common (≥ 1/100 - < 1/10)	**Uncommon** (≥ 1/1000 - < 1/100)	**Rare** (≥ 1/10000 – < 1/1000)	**Very rare** (< 1/10000)	**Not known** (cannot be estimated from the available data)
Infections and infestations				
	Overgrowth of non-susceptible bacteria or fungi e.g. oral and vaginal candidiasis	Pseudomembranous colitis		
Blood and lymphatic system disorders				
				Eosinophilia
Immune system disorders				
	Hypersensitivity ranging from urticaria and mild rash	Anaphylactic reaction including anaphylactic shock		
Metabolism and nutrition disorders				
Decreased appetite				
Psychiatric disorders				
				Hallucinations and confusional state
Nervous system disorders				
		Seizures		Headache, somnolence and dizziness
Eye disorders				
				Visual impairment including diplopia and vision blurred
Ear and labyrinth disorders				
			Tinnitus, reversible hearing loss and deafness*	Vertigo
Cardiac disorders				
		Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), and palpitations		

Common (≥ 1/100 - < 1/10)	**Uncommon** (≥ 1/1000 - < 1/100)	**Rare** (≥ 1/10000 – < 1/1000)	**Very rare** (< 1/10000)	**Not known** (cannot be estimated from the available data)
Vascular disorders				
Thrombophlebitis				Hypotension
Respiratory, thoracic and mediastinal disorders				
				Dyspnoea (including asthmatic states)
Gastrointestinal disorders				
Nausea, flatulence, soft defecation, diarrhoea, vomiting, abdominal cramping and abdominal pain		Pancreatitis	Spastic hypertrophic pyloric stenosis in children	Abdominal discomfort
Hepatobiliary disorders				
	Elevation of certain liver enzymes (GPT, GOT, LDH, AP, γ-GT)	Cholestasis and Jaundice cholestatic	Hepatic dysfunction, with or without jaundice, hepatitis, and/or abnormal liver function test results, hepatomegaly and hepatic failure	
Skin and subcutaneous tissue disorders				
	Erythema, urticarial exanthema, pruritus	Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, allergic oedema/angioedema		
Musculoskeletal and connective tissue disorders				
Muscle spasms		Joint swelling, Rhabdomyolysis	Unmasking and worsening of myasthenia gravis	
Renal and urinary disorders				
			Tubulointerstitial nephritis	
General disorders and administration site conditions				
Local irritation		Pyrexia, irritability during neonatal period		Chest pain, malaise, headache, discomfort

*These disorders are concentration-dependent and are more likely in patients with severe renal and/or hepatic impairment or in high doses or in cases of overdose.

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 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 minimise 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 400 mg erythromycin ethyl succinate, every six hours for seven days.

For treatment of Legionnaires' disease: Although optimal doses have not been established, doses utilised 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:
   0.9% Sodium Chloride Injection, Lactated Ringer's Injection, Normosol-R®.

   For slow continuous infusion:

   Add 20 mL of reconstituted solution to enough diluent to make up to 1000 mL total solution. This is equivalent to a concentration of 1 g of erythromycin per litre (1 mg/mL) or 0.1% infusion.

   For intermittent infusion:

   Add 20 mL of reconstituted solution to enough diluent to make up to 1000 mL total solution. This is equivalent to a concentration of 1 g of erythromycin per litre (1 mg/mL) or 0.1% for an intermittent infusion.

   Add 20 mL of reconstituted solution to enough diluent to make up to 200 mL total solution. This is equivalent to a concentration of 5 mg/mL or 0.5% for an intermittent infusion.

   If it is decided to administer the daily dose as an intermittent infusion, then the erythromycin concentration should not exceed 5 mg/mL and the time of each infusion should be over a minimum of 60 minutes.

3. The following solutions may also be used provided they are first buffered with 8.4% Sodium Bicarbonate Solution (add 0.5 mL 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 overdosage 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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

Amdipharm Mercury (Australia) Pty Ltd
Level 9, 76 Berry Street
North Sydney NSW 2060

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine – Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

4 December 2006

DATE OF MOST RECENT AMENDMENT

4 October 2017

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