Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Erythrocin IV Lactobionate 1 g Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains erythromycin lactobionate equivalent to 1 g of erythromycin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (Powder for sterile concentrate).
A white to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Erythrocin IV Lactobionate is indicated in adults and children for the prophylaxis and treatment of infections caused by erythromycin sensitive organisms.

4.2 Posology and method of administration

Posology

Adults, children and neonates:
Severe and immunocompromised infections;
50 mg/kg/day, preferably by continuous infusion, (equivalent to 4g per day for adults).
Mild to moderate infections (oral route compromised); 25 mg/kg/day.

Elderly:
No special dosage recommendations.

Hepatic impairment
Erythromycin should be used with caution in patients with impaired hepatic function (see sections 4.4 & 5.2).

Method of administration

Bolus injection (IV push) is contraindicated

Continuous infusion of erythromycin lactobionate is preferred due to the slower infusion rate and lower concentration of erythromycin; however, intermittent infusion at intervals not greater than every six hours is also effective.

Erythromycin lactobionate must be administered by continuous or intermittent intravenous infusion only.

Intravenous erythromycin should be replaced by oral erythromycin as soon as possible.

Preparations for administration:

For Intermittent Infusion of 1 gram dose:
Step 1 - add 20 ml of Water for Injections BP to the 1 g vial.
Step 2 - add 20 ml of Step 1 solution to 200-250 ml of Sodium Chloride Intravenous Infusion BP (0.9% Saline). This provides a 0.5%-0.4% solution.

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 between 20 and 60 minutes.

For Continuous Infusion of 1 gram dose:
Step 1 - add 20 ml of Water for Injections BP to the 1 g vial.
Step 2 - add 20 ml of Step 1 solution to 500-1000 ml of Sodium Chloride Intravenous Infusion BP (0.9% Saline). This provides a 0.2%-0.1% infusion.
The infusion should be completed within eight hours of preparation to ensure potency.

Alternative Step 2 diluents:
Compound Sodium Lactate Injection BP (Hartmann's Solution).
Solutions containing glucose may also be used but sodium bicarbonate must first be added as a buffer to ensure neutrality. 5 ml of sterile 8.4% w/v sodium bicarbonate solution will neutralise one litre of: Glucose Injection BP (5%), or of Sodium Chloride and Glucose Injection BP (usually 0.18% sodium chloride and 4.0% glucose).
The stability of solutions of Erythrocin IV Lactobionate is adversely affected below pH 5.5.

For further details please see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substanceor to any of the excipients listed in section 6.1.

Erythromycin is contraindicated in patients taking astemizole, terfenadine, domperidone, cisapride or pimozide.

Erythromycin should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see section 4.4 and 4.5).

Erythromycin should not be given to patients with electrolyte disturbances (hypokalaemia, hypomagnesaemia due to the risk of prolongation of QT interval).

Erythromycin is contraindicated with ergotamine and dihydroergotamine.

Erythromycin must not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see sections 4.4, 4.5 and 4.8).

Concomitant administration of erythromycin and lomitapide is contraindicated (see section 4.5).

Bolus injection (IV push) is contraindicated.

4.4 Special warnings and precautions for use

Cardiovascular Events
Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in patients treated with macrolides including erythromycin (see sections 4.3, 4.5 and 4.8). Fatalities have been reported.

Erythromycin should be used with caution in the following;
Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.
Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.3 and 4.5).

Elderly patients may be more susceptible to drug-associated effects on the QT interval (see section 4.8).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin.

Benzyl alcohol may be added as a preservative. Benzyl alcohol has been reported to be associated with a fatal 'Gasping Syndrome' in premature infants.

Erythromycin is excreted principally by the liver, so caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving potentially hepatotoxic agents. Hepatic dysfunction including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with erythromycin.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening (see section 4.8).

As with other macrolides, rare serious allergic reactions, including acute generalised exanthematous pustulosis (AGEP) have been reported. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including erythromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

There have been reports suggesting erythromycin does not reach the foetus in adequate concentrations 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.

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

Prolonged or repeated use of erythromycin may result in overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, erythromycin should be discontinued and appropriate therapy instituted.

Paediatric population: There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. Epidemiological studies including data from meta-analyses suggest a 2-3-fold increase in the risk of IHPS following exposure to erythromycin in infancy. This risk is highest following exposure to erythromycin during the first 14 days of life. Available data suggests a risk of 2.6% (95% CI: 1.5 -4.2%) following exposure to erythromycin during this time period. The risk of IHPS in the general population is 0.1-0.2%. 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.

There is a risk of 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.

HMG-CoA Reductase Inhibitors: Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (statins). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Erythromycin is contraindicated in patients receiving the HmG-CoA reductase inhibitors lovastatin and simvastatin (see section 4.3 and 4.5). If treatment with erythromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

In situations where the concomitant use of erythromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

Laboratory tests
Erythromycin interferes with the fluorometric determination of urinary catecholamines.

4.5 Interaction with other medicinal products and other forms of interaction

Erythromycin is a moderate inhibitor of CYP3A4 mediated metabolism and P-glycoprotein.

Increases in serum concentrations of the following drugs metabolised by the cytochrome P450 system may occur when administered concurrently with erythromycin: acenocoumarol, alfentanil, astemizole, bromocriptine, carbamazepine, cilostazol, cyclosporin, digoxin, dihydroergotamine, disopyramide, ergotamine, hexobarbitone, methylprednisolone, midazolam, omeprazole, phenytoin, quinidine, rifabutin, sildenafil, tacrolimus, terfenadine, domperidone, theophylline, triazolam, valproate, vinblastine, and antifungals e.g. fluconazole, ketoconazole and itraconazole. Appropriate monitoring should be undertaken and dosage should be adjusted as necessary. Serum concentrations of drugs metabolised by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin. The prescriber should consult appropriate reference sources for additional information.Particular care should be taken with medications known to prolong the QTc interval of the electrocardiogram.

Drugs that induce CYP3A4 (such as rifampicin, phenytoin, carbamazepine, phenobarbital, 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 during two weeks after discontinued treatment with CYP3A4 inducers. Erythromycin should not be used during and two weeks after treatment with CYP3A4 inducers.

HMG-CoA Reductase Inhibitors: Erythromycin is contraindicated in patients receiving the HMG-CoA reductase inhibitors lovastatin and simvastatin (see section 4.3) E erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Concomitant administration of erythromycin with lomitapide is contraindicated due the potential for markedly increased transaminases (see section 4.3).

Contraceptives: some antibiotics may in rare cases decrease the effect of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the intestine and thereby reabsorption of unconjugated steroid. As a result of this plasma levels of active steroid may decrease.

Antihistamine H_1 antagonists: care should be taken in the co-administration of erythromycin with H_1 antagonists such as terfenadine, astemizole and mizolastine due to the alteration of their metabolism by erythromycin.

Erythromycin significantly alters the metabolism of terfenadine, astemizole and pimozide when taken concomitantly. Rare cases of serious, potentially fatal, cardiovascular events, including cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed (see section 4.3 and 4.8).

Anti-bacterial agents: an *in vitro* antagonism exists between erythromycin and the bactericidal beta-lactam antibiotics (e.g. penicillin, cephalosporin). Erythromycin antagonises the action of clindamycin, lincomycin and chloramphenicol. The same applies for streptomycin, tetracyclines and colistin.

Protease inhibitors: in concomitant administration of erythromycin and protease inhibitors, an inhibition of the decomposition of erythromycin has been observed.

Oral anticoagulants: there have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants (e.g. warfarin, rivaroxaban) are used concomitantly.

Triazolobenzodiazepines (such as triazolam and alprazolam) and related benzodiazepines: Erythromycin has been reported to decrease the clearance of triazolam, midazolam and related benzodiazepines, and thus may increase pharmacologic effect of these benzodiazepines.

Corticosteroids: Caution should be exercised in concomitant use of erythromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

Hydroxychloroquine and chloroquine: Erythromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

Post-marketing reports indicate that co-administration of erythromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm and ischaemia of the central nervous system, extremities and other tissues (see section 4.3).

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

Erythromycin use in patients who are receiving high doses of **theophylline** may be associated with an increase in 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 when oral erythromycin is given concurrently with theophylline there is a significant decrease in erythromycin serum concentrations. This decrease could result in sub-therapeutic concentrations of erythromycin.

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

Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients receiving **concurrent verapamil, a calcium channel blocker.**

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

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

4.6 Fertility, pregnancy and lactation

Erythromycin should be used by women during pregnancy or breast-feeding only if clearly needed.

Pregnancy
The available epidemiological studies on the risk of major congenital malformations with use of macrolides including erythromycin during pregnancy provide conflicting results. Some 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.

In a cohort study it was found that there was a modest association between infantile hypertrophic pyloric stenosis (IHPS) and maternal exposure to erythromycin during weeks 28 to birth.

Breast-feeding
Erythromycin is excreted in breast milk, therefore, caution should be exercised when erythromycin is administered to a nursing mother.
There has been a report of a breast-fed infant who developed pyloric stenosis thought to be associated with use of erythromycin by the mother. A cohort study concluded that the use of erythromycin during breast-feeding increased the risk of infantile hypertrophic pyloric stenosis (IHPS).

Fertility
No data available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. dizziness, blurred vision), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention:
Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention:
Rare (≥1/10,000 to <1/1,000)
Not known (cannot be estimated from the available data)

System organ class	Frequency	Undesirable Effects
Blood and lymphatic system disorders	Not known	Eosinophilia
Immune system disorders	Not known	Hypersensitivity, anaphylactic reaction
Psychiatric disorders	Not known	Hallucination
Nervous system disorders	Not known	Dizziness, *confusional state, convulsions, and vertigo
Eye disorders	Not known	Visual impairment (see section 4.4).
Ear and labyrinth disorders	Not known	Deafness**, tinnitus
Cardiac disorders	Not known	Electrocardiogram QT prolonged, torsades de pointes, palpitations and cardiac rhythm disorders including ventricular tachyarrhythmias. Cardiac arrest, ventricular fibrillation (frequency not known)
Vascular disorders	Not known	Hypotension
Gastrointestinal disorders	Rare	Pseudomembranous colitis
	Not known	***Upper abdominal discomfort, nausea, vomiting, diarrhoea, pancreatitis, anorexia, infantile hypertrophic pyloric stenosis.
Hepatobiliary disorders	Not known	Cholestatic hepatitis, jaundice, abnormal hepatic function, hepatomegaly, hepatic failure, hepatitis (see section 4.4).
Skin and subcutaneous tissue disorders	Not known	Rash, pruritus, urticaria, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Not known	Rhabdomyolysis (see sections 4.3, 4.4 and 4.5).
Renal and urinary disorders	Not known	Tubulointerstitial nephritis
General disorders and administration site conditions	Not known	Chest pain, pyrexia, malaise
Investigations	Not known	Increased hepatic enzymes

* There have been isolated reports of transient central nervous system side effects (mentioned in the table); however, a cause and effect relationship has not been established.
** There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency or taking high doses.
*** The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms
Hearing loss, severe nausea, vomiting and diarrhoea.

Management
Gastric lavage, general supportive measures.

In case of overdosage, erythromycin should be discontinued. Erythromycin is not removed by peritoneal dialysis or haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Macrolides
ATC Code: J01FA

Mechanism of action

Erythromycin exerts its antimicrobial action by binding to the 50 S ribosomal sub-unit of susceptible microorganisms and suppresses protein synthesis. It does not affect nucleic acid synthesis. Antagonism has been demonstrated in vitro between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Clinical efficacy and safety
Erythromycin is usually active against most strains of the following organisms both *in vitro* and in clinical infections:

Gram positive bacteria - *Listeria monocytogenes, Corynebacterium diphtheriae* (as an adjunct to antitoxin), *Staphylococci* spp*, Streptococci* spp (including *Enterococci)*.

Gram negative bacteria - *Haemophilus influenzae, Neisseria meningitidis, Neisseria gonorrhoeae, Legionella pneumophila, Moraxella (Branhamella) catarrhalis, Bordetella pertussis*, *Campylobacter* spp.

Mycoplasma - *Mycoplasma pneumoniae, Ureaplasma urealyticum*.

Other organisms - *Treponema pallidum*, *Chlamydia* spp, *Clostridia* spp, L-forms, the agents causing trachoma and lymphogranuloma venereum.

Note: The majority of strains of *Haemophilus influenzae* are susceptible to the concentrations reached after ordinary doses.

5.2 Pharmacokinetic properties

Distribution
Following intravenous infusion, erythromycin is widely distributed throughout body tissues, including lung tissues. Only low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis.

Elimination
In the presence of hepatic function, erythromycin is concentrated in the liver and excreted in the bile. The effect of hepatic dysfunction on excretion of erythromycin by liver into the bile is not known.

5.3 Preclinical safety data

Long-term (2 years) oral studies conducted in rats up to 400 mg/kg/day and in mice up to about 500 mg/kg/day with erythromycin stearate did not provide evidence of tumorigenicity. Mutagenicity studies conducted did not show any genotoxic potential, and there was no apparent effect on male or female fertility in rats treated with erythromycin base by oral gavage at 700 mg/kg/day.
There is no evidence of teratogenicity or any other adverse effect on reproduction in female dosed by oral gavage at 350 mg/kg/day (7 times the human dose) of erythromycin base prior to and during mating, during gestation and through weaning of 2 successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if it is clearly needed. Erythromycin has been reported to cross the placental barrier in humans, but foetal plasma levels are generally low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

3 years.
Once opened the product should be used immediately after reconstitution. When aseptically prepared the solution may be kept for not more than 24 hours if stored under refrigeration at a temperature between 2^{o}C and 8^{o}C.

6.4 Special precautions for storage

Unopened vial: Do not store above 30°C.

For storage conditions after reconstitution, dilution, first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

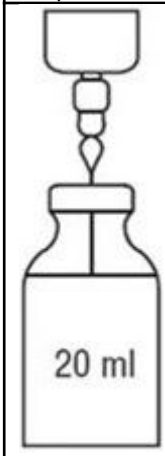
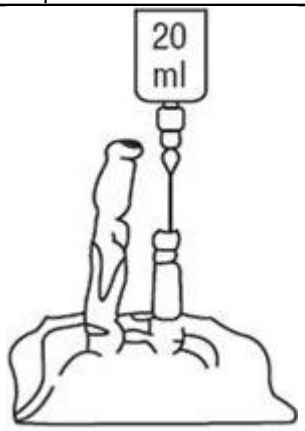
Type I, Ph. Eur., clear vial containing 1 g of erythromycin.

6.6 Special precautions for disposal and other handling

For single use only, discard any unused contents.

The product must be reconstituted (step 1) and then further diluted (step 2) prior to administration.

Preparation of 1 g dose for Intermittent Infusion:

Step 1	Step 2
	
Add 20 ml Water for Injections Ph.Eur to the 1 g vial. No other solvent apart from Water for Injections Ph.Eur should be used to prepare this initial solution.	Add 20 ml of Step 1 solution to 200-250 ml of 0.9% Sodium Chloride Intravenous Infusion BP: The resulting diluted solution contains 5 mg/ml - 4 mg/ml of erythromycin.
	When administering the product by intermittent infusion do not use solution strengths greater than 5 mg/ml and do not use rapid infusion rates – failure to observe these precautions may result in pain along the vain. For detailed instuctions on administration, see section 4.2.

For Continuous Infusion of 1 gram dose:

Add 20 ml of Step 1 solution to 500-1000 ml of 0.9% Sodium Chloride Intravenous Infusion BP. The resulting diluted solution contains 2 mg/ml – 1 mg/ml of erythromycin.

As rapid infusion is more likely to be associated with arrhythmias or hypotension, it is recommended that erythromycin IV is given over a minimum of 60 minutes. A longer period of infusion should be used in patients with risk factors or previous evidence of arrhythmias.

When fully prepared Erythrocin IV Lactobionate 1 g Powder for Concentrate for Solution for Infusion should be virtually free of particulate matter prior to administration.

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
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8 MARKETING AUTHORISATION NUMBER

PA1142/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 January 1980

Date of last renewal: 28 January 2010

10 DATE OF REVISION OF THE TEXT

March 2023