SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erythrocin Lactobionate I.V.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active: erythromycin 1 g/vial

3. PHARMACEUTICAL FORM

Powder for solution for infusion

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the treatment of bacterial infections susceptible to erythromycin and require I.V. treatment.

4.2. Posology and method of administration

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

Elderly: No special dosage recommendations.

Recommended 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.
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.
5ml 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 this medicine is adversely affected below pH 5.5.

For further details please see section 6.6.

4.3. Contraindications

Hypersensitivity to the active substance.

Erythromycin is contraindicated in patients taking simvastatin, tolterodine, mizolastine, amisulpride, 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.

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

Bolus injection (IV push) is an unacceptable route of administration.

This medicine must be administered by continuous or intermittent intravenous infusion only.

4.4. Special warnings and precautions for use

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/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). 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.

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.

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.

<u>Erythromycin should be used with caution in the following;</u>
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.

Carefully consider the balance of benefits and risks before prescribing erythromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

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

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.

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with statins.

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.

4.5. Interaction with other medicinal products and other forms of interaction

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. 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 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.

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 H1 antagonists: care should be taken in the coadministration of erythromycin with H1 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, torsade de pointes and other ventricular arrhythmias have been observed (see sections 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 the pharmacological 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 torsades 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.

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an

increased risk of cardiovascular events and cardiovascular mortality. Because of the potential for a similar risk with other macrolides when used in combination with hydroxychloroquine or chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing erythromycin for any patients taking hydroxychloroquine or chloroquine.

4.6. Fertility, pregnancy and lactation

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.

There is a large amount of data from observational studies performed in several countries on exposure to erythromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period (>24,000 first trimester exposures). While most studies do not suggest an association with adverse fetal effects such as major congenital malformations, cardiovascular malformations or miscarriage, there is limited epidemiological evidence of a small increased risk of major congenital malformations, specifically cardiovascular malformations following first trimester exposure to erythromycin.

Therefore, erythromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding
Erythromycin can be excreted into breast-milk. Caution should be exercised when administering erythromycin to lactating mothers due reports of infantile hypertrophic pyloric stenosis in breast-fed infants.

There have been reports that maternal macrolide antibiotics exposure within 7 weeks of delivery may be associated with a higher risk of infantile hypertrophic pyloric stenosis (IHPS).

Fertility
No data available

4.7. Effects on ability to drive and use machines

No data available.

4.8. Undesirable effects

The list of undesirable effects shown below is presented by system organ class, MedDRA preferred term, and frequency using the following frequency conventions:

Rare (≥1/10,000 to <1/1,000)

Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Rare	Pseudomembranous colitis has been reported rarely in association with erythromycin therapy (see section 4.4).
Blood and lymphatic system disorders	Not known	Eosinophilia
Immune system disorders	Not known	Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred
Psychiatric disorders	Not known	Hallucinations
Nervous system disorders	Not known	*Confusion, seizures and vertigo
Eye disorders	Not known	Mitochondrial Optic Neuropathy
Ear and labyrinth disorders	Not known	**Deafness, tinnitus
Cardiac disorders	Not known	Cardiac arrest, QTc interval prolongation, torsades de pointes, palpitations and cardiac rhythm disorders including ventricular tachyarrhythmias, ventricular fibrillation
Vascular disorders	Not known	Hypotension
Gastrointestinal disorders	Not known	***upper abdominal discomfort, nausea, vomiting, diarrhoea, pancreatitis, anorexia, infantile hypertrophic pyloric stenosis.
Hepatobiliary disorders	Not known	Cholestatic hepatitis, jaundice, hepatic dysfunction, hepatomegaly, hepatic failure, hepatocellular hepatitis (see section 4.4).
Skin and subcutaneous tissue disorders	Not known	Acute generalised exanthematous pustulosis (AGEP) Skin eruptions, pruritus, urticaria, exanthema, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.
Renal and urinary disorders	Not known	Interstitial nephritis
General disorders and administration site conditions	Not known	Chest pain, fever, malaise
Investigations	Not known	Increased liver enzyme values

*There have been isolated reports of transient central nervous system side effects; 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: /https://sideeffects.health.gov.il

4.9. Overdose

Symptoms
Hearing loss, severe nausea, vomiting and diarrhoea.

Management
Gastric lavage, general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01FA01

Mechanism of action
Erythromycin exerts its antimicrobial action by binding to the 50S ribosomal sub-unit of susceptible microorganisms and suppresses protein synthesis. 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.

Susceptibility testing breakpoints:

EUCAST clinical MIC breakpoints for erythromycin (Version 14.0, valid from 2024-01-01):

Pathogen	Susceptible (mg/L)	Resistant (mg/L)
Staphylococcus spp.	≤1	>1
Streptococcus groups A,B,C,G	≤ 0.25	> 0.25
Streptococcus pneumoniae	≤ 0.25	> 0.25
Viridans group streptococci	IE*	IE*
Haemophilus influenzae	Note[1)]	Note[1)]
Moraxella catarrhalis	≤ 0.25	> 0.25
Listeria monocytogenes	≤1	>1
Campylobacter jejuni	≤ 4	> 4
Campylobacter coli	≤ 8	> 8
Corynebacterium diphtheriae and C. ulcerans	≤ 0.06	>0.06
Kingella kingae	≤ 0.5	>0.5
Bacillus spp. except B. anthracis	≤ 0.5	>0.5

1) Clinical evidence for the efficacy of macrolides in H. influenza respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFS) should be used to detect strains with acquired resistance. The ECOFF for erythromycin is 16 mg/l.

**"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug. A MIC with a comment but without an accompanying S, I or R categorisation may be reported.*

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is known and the utility of the agent in at least some types of infections is questionable.

5.2. Pharmacokinetic properties

Following intravenous infusion, erythromycin is widely distributed throughout body tissues, including lung tissues.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None.

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Unopened vial: Do not store above 30°.
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 2ºC and 8ºC.
For reconstitution instructions see enclosed appendix {SPC- 6.6 (step 1 and step 2)}.

6.5. Nature and contents of container

Type I glass tubing vial with grey siliconised cholrobutyl lyophillisation stopper.

6.6. Special precautions for use and disposal

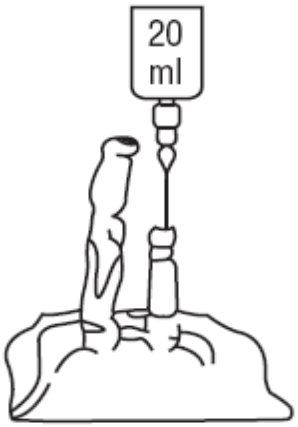
Continuous intravenous infusion with an erythromycin concentration of 1 mg/ml (0.1% solution) is recommended. The infusion should be completed within 8 hours of preparation to ensure potency.

If required, solution strengths up to 5 mg/ml (0.5% solution) may be used, but should not be exceeded. Higher concentrations may result in pain along the vein. Bolus injection is not recommended.

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 vein. For detailed instructions 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 Lactobionate IV 1g powder for concentrate for solution should be virtually free of particulate matter prior to administration.

7. MANUFACTURER

Delpharm Saint Remy
Rue de l'Isle
Saint Remy Sur Avre, 28380

France

8. REGISTRATION HOLDER

Biotis Ltd, 22 Hamelacha St, Rosh Ha'ayin

9. REGISTRATION NUMBER

035-49-25602-05

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