SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Erythromycin 1 g powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains erythromycin lactobionate equivalent to erythromycin 1 g.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White or slightly yellow powder

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Erythromycin is indicated in severe and immunocompromised cases of infections caused by sensitive organisms (see section 5.1) where high blood levels are required at the earliest opportunity or when the oral route is compromised. Erythromycin is indicated for the treatment of the following infections in adults and children including neonates (from birth).

•Upper Respiratory Tract infections: tonsillitis, peritonsillar abscess, pharyngitis, laryngitis, sinusitis, secondary infections in influenza and common colds

•Lower Respiratory Tract infections: tracheitis, acute and chronic bronchitis, pneumonia (lobar pneumonia, bronchopneumonia, primary atypical pneumonia), bronchiectasis, Legionnaire's disease

•Ear infection: otitis media and otitis externa, mastoiditis

•Oral infections: gingivitis, Vincent's angina

•Eye infections: blepharitis

•Skin and soft tissue infections: boils and carbuncles, paronychia, abscesses, pustular acne, impetigo, cellulitis, erysipelas

•Gastrointestinal infections: cholecystitis, staphylococcal enterocolitis

•Prophylaxis: peri-operative secondary infection prophylaxis, severe trauma and burns secondary infection prophylaxis, endocarditis prophylaxis (dental procedures)

•Endocarditis

•Other infections: osteomyelitis, urethritis, gonorrhoea, syphilis, lymphogranulomavenereum, diphtheria, prostatitis, scarlet fever.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Adults: 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.

Newborn infant (birth to 1 month): 10-15mg/kg 3 times daily.

Children: 12.5mg/kg 4 times daily. Doses can be doubled in severe infections.

Elderly: No special dosage recommendations.

Method of administration

Bolus injection (IV) push is contraindicated (see section 4.3)

Continuous infusion of Erythromycin 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 to the 1 g vial.

Step 2 - add 20 ml of Step 1 solution to 200-250 ml of 0.9% (9 mg/ml) sodium chloride solution for injection. 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 to the 1 g vial.

Step 2 - add 20 ml of Step 1 solution to 500-1000 ml of 0.9% (9 mg/ml) sodium chloride solution for injection. 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 (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 (5%), or Sodium Chloride and Glucose Injection (usually 0.18% sodium chloride and 4.0% glucose).

The stability of solutions of Erythromycin is adversely affected below pH 5.5.

For instructions on reconstitution and dilution of Erythromycin before administration, see section 6.6.

4.3 Contraindications

Known hypersensitivity to erythromycin.

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

Erythromycin is contraindicated with ergotamine and dihydroergotamine.

Bolus injection (IV push) is contraindicated.

4.4 Special warnings and precautions for use

Prolonged QTc interval and ventricular arrhythmias have been reported rarely in patients receiving intravenous erythromycin.

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.

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.

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.

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.

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.

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, 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.

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) 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Lactation

Erythromycin is excreted in breast milk, therefore, caution should be exercised when erythromycin is administered to a nursing mother.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

Erythromycin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The list of adverse events is presented by system organ class and frequency using the following frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (≤ 1/10,000), and unknown (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Unknown
Blood and lymphatic system disorders				Eosinophilia
Immune system disorders			Anaphylaxis	Allergic reactions
Psychiatric disorders				Hallucinations
Nervous system disorders				Seizures, confusion, vertigo*
Ear and labyrinth disorders			Reversible hearing loss (mainly in patients with renal insufficiency or high doses)	Deafness, tinnitus
Cardiac disorders				QTc interval prolongation, torsades de pointes, cardiac rhythm disorders including ventricular tachyarrhythmias, palpitations
Vascular disorders				Hypotension
Gastrointestinal disorders	Diarrhoea, nausea			Pseudomembranous colitis (see section 4.4), infantile hypertrophic pyloric stenosis, pancreatitis, vomiting, anorexia, upper abdominal discomfort
Hepatobiliary disorders			Increased liver enzyme values	Hepatic failure, hepatocellular hepatitis (see section 4.4), cholestatic hepatitis, hepatic dysfunction, hepatomegaly, jaundice
Skin and	Skin eruptions	Urticaria		Stevens-Johnson

subcutaneous tissue disorders				syndrome, toxic epidermal necrolysis, erythema multiforme, angioedema, exanthema, pruritus, acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Chest pain, fever, malaise

*There have been isolated reports of transient central nervous system side effects including confusion, seizures and vertigo; however, a cause and effect relationship has not been established.

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 Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms: hearing loss, severe nausea, vomiting and diarrhoea. Treatment: gastric lavage, general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Antibacterial substance for systemic use, ATC code: J01FA01

Erythromycin powder for solution for infusion contains erythromycin lactobionate. Erythromycin lactobionate is a water-soluble salt of erythromycin suitable for intravenous infusion.

Mechanism of action

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

PK/PD relationship

The extent of growth inhibition essentially depends on the duration for which the active substance level is above the minimum inhibition concentration (MIC).

Mechanism of resistance

- Efflux mechanisms can lead to macrolide resistance. Resistance to erythromycin can be brought about by an increase in the number of efflux pumps in the cytoplasm membrane, of which only 14 and 15-member macrolides are affected (known as M-phenotype).

- Methylation of the ribosomal binding sites. Through methylation of the 23S rRNA the affinity to the site of attack can be reduced, resulting in resistance to macrolides (M), lincosamides (L) and group B streptogramins (SB) (MLSB phenotype).

- The enzymatic inactivation of macrolides is only of subordinate clinical relevance.

In the M-phenotype there is full cross-resistance of erythromycin with clarithromycin, roxithromycin or azithromycin. In the MLSB phenotype there is also cross-resistance with clindamycin and streptogramin B. There is partial cross-resistance with the 16-member macrolide spiramycin.

Susceptibility testing breakpoints

The testing of Erythromycin is carried out using the usual dilution series for erythromycin. The following inhibition concentrations for sensitive and resistant pathogens have been determined:

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Susceptibility testing breakpoints

Antimicrobial agent	MIC breakpoint (mg/L)	
	S ≤	R >
Staphylococcus spp.	1	2
Streptococcus groupsA, B, C and G	0.25	0.5
Streptococcus pneumoniae	0.25	0.5
Haemophilus influenzae	0.5	16
Moraxella catarrhalis	0.25	0.5
Listeria monocytogenes	1	1
Campylobacter jejuni	4	4
Campylobacter coli	8	8

Microbiological susceptibility

The prevalence of acquired resistance may vary in certain species geographically and change over time, hence local information on resistance is desirable, particularly when treating severe infections. The table below can provide only an indication of the probability with which microorganisms are sensitive or insensitive to erythromycin.

Table : Antibacterial spectrum of erythromycin

Commonly susceptible species	Streptococci and pneumococci *Staphylococcus aureus* and *coagulase-negative staphylococci* *Arcanobacterium haemolyticum* *Corynebacterium diphteriae* *Moraxella catarrhalis* *Bordetella pertussis* *Legionella pneumophila* *Campylobacter* *Chlamydia trachomatis, pneumoniae* and *psittaci* *Mycoplasma pneumoniae* *Ureaplasma urealyticum* *Clostridium perfringens*
Species for which acquired resistance may be a problem	*Haemophilus influenzae* and *parainfluenzae*
Inherently resistant organisms	Enterococci *Pasteurella multocida* *Gram-negative intestinal bacteria* and *Pseudomonas* *Clostridium difficile* Anaerobic gram-negative rods *Mycoplasma hominis*

Resistance is found (1-10%) in beta-haemolytic streptococci, pneumococci and Staphylococcus aureus and is common (>10%) in coagulase-negative staphylococci.

Cross-resistance occurs between all macrolides and azithromycin. Some cross-resistance between macrolides and clindamycin.

Erythromycin resistance in streptococci and pneumococci is common in some parts of Europe.

5.2 Pharmacokinetic properties

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

Little metabolism occurs and only about 5% is excreted in the urine. It is excreted principally by the liver.

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 SmPC.

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

Unopened: 3 years.

After reconstitution:

After reconstitution, chemical and physical in-use stability in water for injection has been demonstrated for 24 hours when stored at room temperature and for 14 days when stored in a refrigerator at 2-8° C.

After reconstitution and dilution:

After reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature when the solution is diluted in 0.9% (9 mg/ml) sodium chloride solution for injection or Glucose 5% and for 12 hours at room temperature when the solution is diluted in Hartman's solution.

From a microbiological point of view, once opened, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

This product does not require any special storage conditions.

For storage conditions of the reconstituted/diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass vial type I with rubber closure type I. 1 vial contains erythromycin lactobionate equivalent to erythromycin 1 g.

1 x 1 g powder for solution for infusion

10 x 1 g powder for solution for infusion

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Continuous intravenous infusion with an erythromycin concentration of 1mg/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 5mg/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.

7 MARKETING AUTHORISATION HOLDER

Stragen UK Ltd.

Castle Court

41 London Road

Reigate

Surrey

RH2 9RJ

8 MARKETING AUTHORISATION NUMBER(S)

PL21844/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/05/2016

10 DATE OF REVISION OF THE TEXT

17/01/2018