

# Erythromycin 1g Powder for Solution for Infusion

Summary of Product Characteristics Updated 22-Jun-2022 | Panpharma UK Ltd

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## 1. Name of the medicinal product

ERYTHROMYCIN 1 g, powder for solution for infusion

## 2. Qualitative and quantitative composition

Erythromycin..... 1g

(as Erythromycin Lactobionate)

For 1 vial

For the complete list of excipients, see section 6.1.

## 3. Pharmaceutical form

White or slightly yellow hygroscopic powder for solution for infusion

## 4. Clinical particulars

### 4.1 Therapeutic indications

Erythromycin Panpharma is indicated for treatment of the following appropriately diagnosed bacterial infections in adults and children caused by susceptible strains of organisms (see section 5.1) when oral administration is not possible or insufficient.

- Conjunctivitis,
- Pneumonia caused by atypical agents,
- Whooping cough,

- Urogenital infections,
- Severe gastroenteritis ,
- Diphtheria,
- Lymphogranuloma venereum.

Erythromycin is also indicated for the treatment of the following infections in patients with hypersensitivity to beta-lactams or when beta-lactams are not appropriate for other reasons:

- Otitis media in severe cases,
- Community acquired pneumonia (see section 4.4),
- Skin and soft tissue infections,
- Acute bacterial exacerbation of chronic bronchitis,

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

## 4.2 Posology and method of administration

Intravenous therapy must be replaced by oral administration at the appropriate time.

### **Posology**

Adults and children over 12 years old or weighing > 40 kg

The usual dose is 1 to 2 g per day equivalent to 25 mg/kg/day in divided doses (generally 3-4 single doses).

#### *Severe infections*

Dosage can be increased up to 4 g per day equivalent to 50 mg/kg/day in severe infections.

The maximum daily dose is 4 g.

Children up to 12 years old or weighing ≤ 40 kg

1 months to up to 12 years old: The daily dose for infants and children up to 12 years old for most infections is 15-20 mg of erythromycin/kg of body weight divided over 3-4 single doses. This dose may be doubled depending on the indication.

Term newborn infants (birth to 1 month)

10-15mg/kg/day divided over 3 singles doses

Renal/hepatic impairment

### **Patients with impaired hepatic function:**

In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile. Although the effect of hepatic dysfunction on the excretion of erythromycin and its half-life in such patients is not known, caution should be exercised in administering the antibiotic in such cases particularly if patients with acute hepatic insufficiency receive high doses of erythromycin. In that case, monitoring of serum levels and dosage reduction will be required.

### **Patients with impaired renal function:**

The low proportion of renal excretion would suggest that dosage modification in patients with impaired renal function (slightly or moderately impaired renal function with creatinine clearance levels higher than 10ml/min) may not be necessary.

For patients with moderate to severely impaired renal function, however, toxicity has been reported and dosage adjustment in these cases may be warranted:

- Administration of doses of ≥ 4 g/day may increase the risk for the development of erythromycin-induced hearing loss in elderly patients, particularly those with reduced renal or hepatic function.
- In moderate to severely impaired renal function (with a level of serum creatinine of 2.0 mg/dl, kidney failure with anuria), the maximum daily dose for adolescents over 14 years old and adults (with a body weight over 50 kg) is 2 g erythromycin per day.
- In patients with severe renal insufficiency (creatinine clearance levels lower than 10ml/min), the erythromycin dose must be reduced to 50% to 75% of the normal dose, to be administered in accordance with the usual treatment regimen. The maximum daily dose must not exceed 2g.

Erythromycin is not removed by haemodialysis or peritoneal dialysis. For patients who have regular dialysis, an additional dose is therefore not recommended.

### Elderly

Use adult dosage with care. Elderly patients, particularly those with reduced renal or hepatic function may be at increased risk for developing erythromycin-induced hearing loss, when erythromycin doses of 4 g/day or higher are

given.

### **Method of administration**

#### *Precautions to be taken before handling or administering the medicinal product*

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Erythromycin can be administered in continuous or intermittent infusion.

The infusion should be administered over 60 minutes as a rapid infusion is more likely to be associated with local irritative effects as well as QT interval prolongation, arrhythmias or hypotension. A longer period of infusion should be used in patients with risk factors or previous evidence of arrhythmias. Not less than 200 ml of diluent should be used for preparing intermittent I.V. solutions so as to minimise venous irritation.

The erythromycin concentration should not exceed 5mg per ml and an erythromycin concentration of 1mg/ml (0.1% solution) is recommended.

Erythromycin should only be administered intravenously. Intra-arterial injection is strictly contraindicated. It can lead to angiospasm with ischaemia. Intramuscular administration and IV bolus injection are also contraindicated.

Intravenous therapy should be replaced by oral administration after 2-7 days. In the interest of sustaining successful treatment, erythromycin should be continued for a further 2-3 days after symptoms have disappeared.

### **4.3 Contraindications**

Patients with known hypersensitivity to erythromycin, to any of the drug's excipients listed in section 6.1, or to other macrolide antibiotics.

Concomitant treatment with astemizole, terfenadine, disopyramide, cisapride, pimozide, ergot alkaloids (such as ergotamine and dihydroergotamine) simvastatin, atorvastatin or lovastatin.

Patients with severe hepatic impairment, or patients with severe decompensated heart failure (NYHA IV).

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)

Concomitant use with drugs which likewise can lead to QT interval prolongation, such as anti-arrhythmics classes IA and III, certain neuroleptics, tri- and tetracyclic antidepressants, arsenic trioxide, methadone and budipine, certain fluoroquinolones, Imidazole antifungal and anti-malarial drugs such as IV pentamidine.

### **4.4 Special warnings and precautions for use**

It is generally not recommended to combine erythromycin with:

Alfuzosine, dopaminergic rye ergot alkaloids, buspirone, carbamazepine, cyclosporine, colchicine, disopyramide, ebastine, halofantrine, lumefantrine, tacrolimus, theophylline, tolterodine, triazolam.

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).

#### ***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.

Appropriate laboratory tests, including if necessary, electrolyte analyses, must be carried out when there are risk factors for electrolyte disturbances, such as diuretic and laxative medication, vomiting, diarrhoea, insulin use in emergency situations, kidney disease or anorexic conditions, since electrolyte disturbances promote the likelihood of arrhythmias.

### ***Hypersensitivity reactions***

Serious, life-threatening allergic reactions may occur during treatment with erythromycin, such as serious skin conditions like urticarial, erythema multiforme exudativum, Stevens-Johnson-syndrome or toxic epidermal necrolysis (especially in children of all ages), angioedema or anaphylaxis. Superinfection may occur with prolonged use, giving rise to overgrowth of non-susceptible organisms.

### ***Patients treated with corticosteroids or corticotrophins***

Caution must be exercised in the administration of parenteral fluids, especially those containing sodium ions, to patients receiving corticosteroids or corticotrophins.

### ***Myasthenia gravis***

There have been reports that erythromycin can exacerbate the symptoms of myasthenia gravis which may result in life threatening weakness of respiratory muscles. Adequate counter measures should be taken at any sign of respiratory distress (see section 4.8)

### ***Pneumonia***

In case of pneumonia by *Streptococcus pneumoniae*, erythromycin should be used only in patients with hypersensitivity to beta-lactams or when beta-lactams are not appropriate for other reasons. Otherwise, erythromycin can be used as first-line therapy only in case of pneumonia caused by atypical agents.

### ***Clostridium difficile-associated diarrhoea (CDAD)/ Pseudomembranous colitis***

As with other broad spectrum antibiotics, pseudomembranous colitis has been reported rarely with erythromycin, in varying degrees of severity from light diarrhoea to life-threatening colitis.

Practically all antibiotics, including erythromycin, are associated with Clostridium difficile-associated diarrhoea (CDAD). CDAD can occur up to two months after treatment with erythromycin as light diarrhoea to lethally progressive colitis. In this case, termination of treatment, depending on the indication, should be considered, and if necessary, appropriate treatment should be initiated (e.g. administration of special antibiotics/chemotherapeutic agents whose effectiveness have been clinically proven). Drugs, which inhibit peristalsis, are contraindicated in the case of pseudomembranous colitis.

### ***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 infection with Bordetella pertussis or Chlamydia trachomatis), the benefit of erythromycin therapy needs to be carefully considered against the potential risk of developing IHPS. Patients or their caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

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.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### **Effects of erythromycin on other medicinal products**

Erythromycin is an inhibitor of CYP3A4 and the transport protein P-glycoprotein. The extent of inhibition with different CYP3A4 substrates is difficult to predict. Erythromycin should therefore not be used during treatment with CYP3A4 substrates unless the plasma concentrations, effects or side effects of the substrate can be closely followed. A dose reduction of other medicinal products that are metabolised by CYP3A4 can be necessary and combination with erythromycin should take place with caution (e.g. acenocoumarol, alfentanil, bromocriptine, cilostazole, cyclosporine, hexobarbiton, colchicine, methylprednisolone, midazolam, omeprazole, tacrolimus, valproate, vinblastine, antimycotics such as fluconazole, ketoconazole and itraconazole). Alternatively, the treatment with CYP3A4 substrates should be discontinued during treatment with erythromycin.

### ***Medicinal products that may prolong the QT interval***

Erythromycin affects the metabolism of terfenadine, astemizole and pimozone during concomitant administration. Rare cases of severe, potentially fatal cardiovascular events such as cardiac arrest, torsades de pointes and other ventricular

arrhythmias have been observed and therefore concomitant administration of these medicinal products is contraindicated (see section 4.3).

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 torsades de pointes. Similar effects have been observed with concomitant administration of disopyramide and erythromycin and may be expected also in patients taking astemizole or pimozide. Concomitant administration with astemizole, cisapride, disopyramide and pimozide is contraindicated (see section 4.3).

Erythromycin may inhibit the metabolism of quinidine resulting in a 40% increase in C<sub>max</sub> in healthy volunteers. There are case reports of increased plasma concentrations and torsades de pointes. In case of concomitant treatment with erythromycin the plasma levels of quinidine should be controlled.

Caution is recommended when erythromycin is given to patients treated with other medicinal products that may prolong the QT interval (see section 4.4).

#### *Sildenafil*

Data suggest that erythromycin inhibits the metabolism of sildenafil. A starting dose of 25 mg sildenafil should be considered.

#### *Benzodiazepines*

Erythromycin has been reported to decrease clearance of triazolam, alprazolam, clozapine and related benzodiazepines and thereby increasing the pharmacological effect of these medicinal products. In healthy volunteers pretreated with erythromycin the absorption of zopiclone is faster resulting in higher plasma concentrations and more pronounced hypnotic effect compared to controls.

#### *Theophylline*

Concomitant treatment with erythromycin and high doses of theophylline may result in increased plasma theophylline levels and potential theophylline toxicity, probably due to inhibition of metabolism. In case of concomitant treatment plasma levels of theophylline should be followed in order to avoid toxic plasma levels (dose reduction). The erythromycin plasma concentrations may be reduced in case oral erythromycin is given together with theophylline, possibly resulting in subtherapeutic erythromycin levels.

#### *Oral anticoagulants*

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

#### *Fexofenadine*

In case of concomitant treatment with erythromycin and fexofenadine plasma concentrations of fexofenadine increase 2-3-fold, probably due to increased absorption.

#### *Statins*

Erythromycin inhibits the metabolism of several HMG-CoA reductase inhibitors resulting in increased plasma concentrations of these medicinal products. Erythromycin also increases the plasma concentrations of simvastatin acid (5-fold). Rare cases of rhabdomyolysis, associated with elevated plasma levels, have been reported during concomitant treatment with clarithromycin and lovastatin or simvastatin. Erythromycin must not be used concomitantly with simvastatin, atorvastatin or lovastatin. Treatment with these medicinal products must be discontinued during treatment with erythromycin.

#### *Ergot alkaloids (e.g. ergotamine and dihydroergotamine)*

There are case reports of clinical ergotism, characterised by vasospasm and ischaemia in CNS, extremities and other tissues, due to elevated plasma levels of ergot alkaloids during concomitant treatment with macrolide antibiotics. The combination is contraindicated (see section 4.3).

#### *Digoxin*

Concomitant treatment with erythromycin and digoxin may result in elevated plasma digoxin levels. Control of plasma levels should be considered during initiation and termination of erythromycin treatment. Dose adjustment may be necessary.

Hypotension, bradyarrhythmia and lactic acidosis has been observed in patients concomitantly treated with the calcium channel blocker verapamil.

#### Effects of other medicinal products on the pharmacokinetics of erythromycin

Erythromycin is metabolised by CYP3A4. Thus, strong inhibitors of this enzyme may inhibit the metabolism of erythromycin resulting in elevated plasma levels.

Medicinal products that induce CYP3A4 (such as rifampin, phenytoin, carbamazepine, Phenobarbital, St. John's Wort (*Hypericum perforatum*)) can induce the metabolism of erythromycin. This may lead to subtherapeutic levels of erythromycin and consequently may reduce the effect. The induction is gradually reduced over a period of 2 weeks

following discontinuation of treatment with CYP3A4 inducers. Erythromycin should not be used during treatment with CYP3A4 inducers and 2 weeks following discontinuation of therapy.

Cimetidine may inhibit the metabolism of erythromycin resulting in elevated plasma levels.

During concomitant treatment with erythromycin and protease inhibitors inhibition of erythromycin metabolism has been observed.

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

There are no animal reproductive toxicology studies with erythromycin available, but studies with other macrolides, that similar to erythromycin are potent hERG-channels blockers, have shown embryonic death and malformations (including cardiovascular defects and cleft palate). Mechanistic studies have shown that substances blocking the hERG-channel cause cardiovascular defects and embryonic death by inducing arrhythmia in the foetus.

There are no appropriately controlled studies in pregnant women. Erythromycin crosses the placenta and gives rise to foetal plasma levels which are approximately 5-20 % of maternal limits. 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.

### Breastfeeding

Erythromycin is not recommended for nursing mothers unless the expected benefits outweigh the potential risks. In lactating women, erythromycin is secreted into breast milk in quantities of between 0.5 and 6.2 micrograms/ml. These quantities are not known to be harmful. About 50% of the drug crosses into the mother's milk and can cause gastrointestinal disorders in the infant, but possibly also the formation of pyloric stenosis. Furthermore, sensitivity or infection with blastomycetes is also possible.

The benefits and risks of use during lactation must be carefully considered.

### Fertility

No data exists on the effect of erythromycin on fertility in human subjects. Animal studies showed that erythromycin has no teratogenic effects.

## 4.7 Effects on ability to drive and use machines

The occurrence of side effects of erythromycin may affect the ability to drive and use machines.

Experience to date shows that erythromycin has negligible influence on the ability to concentrate and react.

## 4.8 Undesirable effects

### Summary of the safety profile

The adverse event profile presented below is based on post-marketing experience. The most frequently reported adverse reactions were gastrointestinal disorders mostly mild in nature in the forms of anorexia, retching, vomiting, abdominal pains, nausea, flatulence, discomfort, cramps, soft stools or diarrhoea.

### Tabulated list of adverse reactions

Adverse reactions from post-marketing experience are listed in the following table per System Organ Class and per frequency. The frequency is defined as follow: Very common ( $\geq 1/10$ ) common ( $\geq 1/100$ - $<1/10$ ) uncommon ( $\geq 1/1000$ - $<1/100$ ) rare ( $\geq 1/10000$ - $<1/1000$ ) very rare ( $<1/10000$ ) not known (Frequency cannot be estimated from the available data).

MedDRA SOC	Frequency category				
	Common	Uncommon	Rare	Very rare	Not known

<b>Infections and infestations</b>		Superinfections caused by resistant bacteria or fungi, e. g. oral and vaginal candidiasis	Pseudomembranous colitis		
<b>Blood and lymphatic system disorders</b>					Eosinophilia
<b>Immune system disorders</b>		Allergic reactions	Allergic oedema/angioedema, anaphylactic reaction including anaphylactic shock, anaphylaxis		
<b>Metabolism and nutrition disorders</b>			Anorexia		
<b>Psychiatric disorders</b>					Hallucinations
<b>Nervous system disorders</b>				Unmasking or worsening of Myasthenia gravis	Transient central nervous system disorders, such as state of confusion, epileptic seizures, convulsions, hallucinations, headaches, sleepiness and vertigo.
<b>Eye disorders</b>					Visual disturbances, including diplopia and blurred vision
<b>Ear and labyrinth disorders</b>				Tinnitus and mainly transient loss of hearing or deafness, primarily in patients with renal and/or hepatic impairment or patients who are treated with high doses	
<b>Cardiac disorders</b>					Palpitation and cardiac arrhythmias, atrioventricular block, QT interval prolongation, ventricular extra systole, ventricular arrhythmia

					(torsades des pointes), and ventricular tachycardias particularly in patients, who have already shown a prolonged QT interval on an ECG or concomitantly use potentially pro-arrhythmic or QT-interval influencing substances, cardiac arrest, ventricular fibrillation
<b>Vascular disorders</b>		Thrombophlebitis			Hypotension
<b>Respiratory, thoracic and mediastinal disorders</b>					Dyspnoea (including asthmatic conditions)
<b>Gastro- intestinal disorders</b>	Gastrointestinal disorders mostly mild in nature in the forms of anorexia, retching, vomiting, abdominal pains, nausea, flatulence, discomfort, cramps, soft stools or diarrhoea.		Infantile hypertrophic pyloric stenosis (IHPS); pancreatitis		
<b>Hepatobiliary disorders</b>			Cholestasis and cholestatic jaundice, especially in long-term treatment (2-3 weeks) and especially in pre-existing liver damage, and in repeat treatments and in patients with allergies	Cholestatic hepatitis or hepatitis-like symptoms, hepatomegaly, liver failure, hepatic dysfunction,	
<b>Skin and subcutaneous tissue disorders</b>		Hyperaemia and urticarial exanthema, pruritus, skin eruptions		Erythema multiforme exudativum, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome, especially in children of all ages)	Acute generalised exanthema-tous pustulosis (AGEP)



<b>Musculoskeletal and connective tissue disorders</b>			Swollen joints		
<b>Renal and urinary disorders</b>				Interstitial nephritis	
<b>General disorders and administration site conditions</b>		Pain and/or irritation at the site of injection	Drug fever		Chest pain, fever, malaise
<b>Investigations</b>		Increase in certain liver enzymes (transaminases (ALT and AST), LDH, alkaline phosphatase, Y-GT and bilirubin			

#### Paediatric population

Vomiting or irritability in connection with meals in infants. Instances of infantile hypertrophic pyloric stenosis (IHPS) have appeared in infants after treatment with erythromycin

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store

## 4.9 Overdose

The toxicity is low. Overdosage may be associated with ototoxicity, hearing loss, cholestasis, ventricular arrhythmias, severe nausea, vomiting and diarrhoea. The symptoms are typically reversible and will disappear when treatment with erythromycin is discontinued. No specific treatment has been proposed other than general supportive measures. In the event of an overdose, treatment with erythromycin should be paused or terminated depending on the symptoms. Erythromycin cannot be removed with peritoneal or haemodialysis.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIBACTERIAL FOR SYSTEMIC USE ATC code: J01FA01

Erythromycin is a semi-synthetic macrolide with a 14-membered lactone ring.

#### Mode of action

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

Erythromycin does not bind to cytoplasmic membranes of the host cells. This is a possible explanation of its low toxicity and safety record.

Erythromycin is bacteriostatic and bactericidal depending on its concentration and the type of organism. It inhibits protein synthesis by binding to ribosomal subunits, inhibiting translocation of aminoacyl transfer RNA and inhibiting polypeptide synthesis without causing any alteration in the nucleic acid cycle.

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

#### Resistance:

#### Known resistance mechanisms in pathogens relevant to the indications:

- Efflux mechanisms can lead to macrolide resistance. Resistance to erythromycin can be caused by an increase in the number of efflux pumps in the cytoplasm membrane, which only affects the 14- and 15-membered macrolides (so-called "M"-phenotype).
- Methylation of the ribosomal binding sites. The affinity to the target site can be reduced by methylation of the 23S rRNS, resulting in resistance to macrolides (M), lincosamides (L) and Group B Strep gram positive (SB) (so-called "MLSB"-phenotype).

- The enzymatic inactivation of macrolides is only of minor clinical significance.

There is complete cross-resistance in the "M"-phenotype of erythromycin with clarithromycin, roxithromycin or azithromycin. In the "MLSS"-phenotype, there is additional cross-resistance to clindamycin and Group B Strep gram positive bacteria. There is a partial cross resistance to the 16-membered macrolide, spiramycin.

Susceptibility testing breakpoints:

The testing of erythromycin is made using the usual dilution series for erythromycin. As a result, minimal inhibitory concentrations (MIC) for susceptible and resistant bacteria were identified. The recommended EUCAST (European Committee on Antimicrobial Susceptibility Testing) MIC breakpoints for erythromycin are presented below in the table for MIC testing (mg/L):

**EUCAST clinical MIC breakpoints for erythromycin (version 9.0, valid from 2019-01-01):**

Pathogen	Susceptible (mg/L)	Resistant (mg/L)
<i>Staphylococcus spp.</i>	≤1	>2
<i>Streptococcus groups A,B,C,G</i>	≤ 0.25	> 0.5
<i>Streptococcus pneumoniae</i>	≤ 0.25	> 0.5
<i>Haemophilus influenzae</i>	Note <sup>1)</sup>	Note <sup>1)</sup>
<i>Moraxella catarrhalis</i>	≤ 0.25	> 0.5
<i>Campylobacter jejuni</i>	≤ 4	> 4
<i>Campylobacter coli</i>	≤ 8	> 8
Non species related breakpoints	IE*	IE*

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.

Usually susceptible species:

**Aerobic Gram-positive bacteria**

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Streptococcus pyogenes*

**Aerobic Gram-negative bacteria**

*Bordetella pertussis*

*Campylobacter jejuni*

*Moraxella catarrhalis*

**Other bacteria**

*Chlamydia trachomatis*

*Chlamydia pneumoniae*

*Chlamydia psittaci*

*Legionella pneumophila*

*Mycoplasma pneumoniae*

Species for which acquired resistance may be a problem:

**Aerobic Gram-positive bacteria**

*Staphylococcus aureus* (Methicillin-susceptibility)

*Streptococcus pneumoniae*

#### **Aerobic Gram-negative bacteria**

*Haemophilus influenzae*

#### **Other bacteria**

*Treponema pallidum*

#### **Inherently resistant species:**

#### **Aerobic Gram-negative bacteria**

*Escherichia coli*

*Klebsiella spp.*

*Pseudomonas aeruginosa*

#### **Aerobic Gram-positive bacteria**

*Staphylococcus aureus* (Methicillin-resistant)+

### **5.2 Pharmacokinetic properties**

#### **Distribution**

The apparent volume of distribution of erythromycin is around 45% of body weight in normal subjects. This large distribution volume is consistent with the extensive tissue penetration of erythromycin.

Erythromycin diffuses readily into most body fluids, except the cerebrospinal fluid. However, in cases of meningeal inflammation, higher concentrations are apparent.

#### **Biotransformation**

In studies using rabbit microsomes it has been shown that erythromycin is demethylated to des-N-methyl erythromycin and formaldehyde.

#### **Elimination**

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

From 12% to 15% of intravenously administered erythromycin is excreted in active form in the urine.

The drug is also excreted in the faeces.

#### **Pharmacokinetic/pharmacodynamic relationship(s)**

The plasma elimination half-life in patients with normal renal function is about 2 hours. In severe renal impairment the half-life may be prolonged to between 4 and 7 hours.

### **5.3 Preclinical safety data**

The acute and chronic oral toxicity of erythromycin is low.

No evidence has been verified of teratogenicity or any other adverse reaction in the reproduction of female rats, who received oral tube administration of 350 mg/kg/day (7 times the human dose) of Erythromycin base prior to or during mating, pregnancy and during weaning.

No evidence was observed of teratogenicity or embryo toxicity when erythromycin base was administered by oral tube to pregnant female rats and mice at a dose of 700 mg/kg/day (14 times the human dose), and to pregnant female rabbits at a dose of 125 mg/kg/day (2.5 times the human dose).

A slight reduction was detected in birth weights when female rats were treated prior to mating, during mating, pregnancy and breastfeeding, with a high oral dose of 700 mg/kg/day of erythromycin base; the weights of the litter were comparable to those of the controls by the time of weaning. No evidence of teratogenicity or effects on reproduction were observed at this dose. When administered during the final stage of pregnancy and breastfeeding, this dose of 700 mg/kg/day (14 times the human dose) did not result in any adverse effects in birth weight, growth or survival of the litter.

#### **Carcinogenicity, Mutagenicity, Changes in Fertility**

Long-term studies (2 years) with the oral formulation of erythromycin stearate, conducted in rats up to almost 400 mg/kg/day and in mice up to almost 500 mg/kg/day, did not reveal any evidence of tumorigenicity.

The mutagenicity studies conducted did not reveal any genotoxic potential, and no evident effects were observed on the fertility of male or female rats treated with 700 mg/kg/day of erythromycin base via oral tube.

## 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 6.6.

Erythromycin lactobionate in solution does not blend, mainly because of the pH shifts, with  $\beta$ -lactam antibiotics, aminoglycosides, tetracyclines, Chloramphenicol, Colistin, Aminophylline, barbiturates, Diphenylhydantoin, Heparin, Phenothiazine, riboflavin (vitamin B2), vitamin B6 and vitamin C. Therefore, Erythromycin. should not be mixed with the named drugs in an infusion solution.

The addition of other solutions, which alter the range from pH 6-8, reduces the stability of erythromycin lactobionate.

**Attention:** Sodium chloride solutions or other solutions which contain inorganic salts should not be used to prepare the stock solution (see section 6.6 "Special precautions for disposal and other handling"), as it may cause precipitation.

### 6.3 Shelf life

36 months

For the reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 h in the refrigerator (2 to 8°C).

For the diluted solution: Chemical and physical in-use stability has been demonstrated for 24 h in the refrigerator (2 to 8°C).

From a microbiological point of view, 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 in the refrigerator, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

No special storage condition.

For storage conditions after reconstitution of the medicinal product, see section 6.3 and section 6.6.

### 6.5 Nature and contents of container

Colourless type III vials clear glass vial. Pack size of 1, 10 or 25 glass vials.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Each vial is for single use only.

Erythromycin is reconstituted and then further diluted prior to infusion.

Preparation of the solution for administration:

Two steps are required, reconstitution **and** dilution.

**1. Reconstitution:** For this step, do not use 0.9% sodium chloride solution.

- a. To allow a proper dissolution, gently agitate the vial to loosen powder contents prior to reconstitution.
- b. Prepare an initial solution corresponding to 50 mg/ml of erythromycin base by adding 20 ml of water for injections to the content of the vial of Erythromycin Panpharma 1 g. When adding the solvent, please make sure that it makes contact with all the walls of the vials (by holding the vial horizontally for example).
- c. Shake abundantly until complete dissolution. The dissolution can be difficult and take a few minutes.

The reconstituted solution can be kept in the refrigerator for 24 hours.

#### **2. Dilution**

Only a 0.9% sodium chloride solution or 5% glucose solution should be used.

- For intermittent infusion: The solution is prepared by mixing the content of the reconstituted vial of Erythromycin Panpharma 1 g (20 ml) to 200 ml or to 500 ml of one of the dilution solvents, giving a final concentration for the diluted solution of respectively 5 mg/ml or 2 mg/ml.

- For continuous infusion: The solution is prepared by mixing the content of the reconstituted vial of Erythromycin Panpharma 1 g (20 ml) to 500 ml or to 1000 ml of one of the dilution solvents, giving a final concentration for the diluted solution of respectively 2 mg/ml or 1 mg/ml.

The diluted solution can be kept in the refrigerator for 24 hours. The diluted solution is administered without addition any other substance whatsoever.

In children, adjust the quantity of initial solution for dilution and the volume of infusion to the dosage chosen according to the child's weight.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. Marketing authorisation holder**

**PANPHARMA**

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FRANCE

## **8. Marketing authorisation number(s)**

PL 44124/0002

## **9. Date of first authorisation/renewal of the authorisation**

27 June 2016

## **10. Date of revision of the text**

April 2022

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