

**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0437/025/001**

Case No: 2055150

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**HOSPIRA UK Ltd**

**Queensway, Royal Leamington Spa, Warwickshire CV31 3RW, United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Erythromycin 1g Powder for Concentrate for Solution for Infusion**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **17/09/2008**.

Signed on behalf of the Irish Medicines Board this

\_\_\_\_\_

A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Erythromycin 1g Powder for Concentrate for Solution for Infusion.

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial, before reconstitution contains:

Erythromycin 1 g (as lactobionate)

When reconstituted as directed in section 6.6 (*Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product*), each vial provides a concentrate for solution for infusion containing 50 mg/ml erythromycin (as lactobionate).

For full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.  
A white powder or plug.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

1. Upper respiratory tract infections (tonsillitis, pharyngitis, sinusitis, secondary bacterial infections).
2. Lower respiratory tract infections (pneumonia, bronchitis, primary atypical pneumonia, Legionnaire's disease).
3. Skin and soft tissue infections (furunculosis, erysipelas).
4. Other infections - diphtheria carriers and cases as an adjunct to antitoxin, syphilis and gonorrhoea (in cases of penicillin allergy), subacute bacterial endocarditis, otitis media.

##### 4.2 Posology and method of administration

Intravenous administration of erythromycin is suitable to patients who are unable to tolerate oral medication or when it is necessary to produce a high blood concentration to control severe infections. Oral administration should replace parenteral administration as soon as practicable.

Due to the local irritative effects of erythromycin as well as reports of QT interval prolongation and ventricular arrhythmias (some of which have been fatal) being associated with elevated serum concentrations of erythromycin, the drug must not be administered rapidly by direct intravenous injection (IV push).

For continuous I.V. infusion the concentrated solution should be diluted to a concentration of 1mg per ml. 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.

For intermittent I.V. infusion the appropriate daily dose can be given as 4 doses once every 6 hours. The erythromycin concentration should not exceed 5mg per ml and the infusion should be administered over 60 minutes, as a rapid infusion is more likely to be associated with arrhythmias or hypotension. A longer period of infusion should be used in patients with risk factors or previous evidence of arrhythmias. Not less than 100ml of diluent should be used for preparing intermittent I.V. solutions.

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

**Adults:** The usual adult dose is the equivalent of 25-50mg/kg per day in divided doses of erythromycin, by intravenous infusion every 6 hours, or the equivalent of 1 to 2g of erythromycin daily by intermittent intravenous infusion over 20 to 60 minutes every 6 hours or by infusion over 24 hours. The equivalent of 4 gram daily has been recommended for severe infections.

Small volume I.V. infusion, minimum volume 100ml, is the preferred method so as to minimise venous irritation.

**Children:** 25-50mg per kg by intravenous injection, daily in divided doses.

**Elderly:** Use adult dosage with care, taking into consideration any impairment in liver or biliary functions.

**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.

**Patients with impaired renal function:** The low proportion of renal excretion would suggest that dosage modification in patients with impaired renal function may not be necessary. In severely impaired patients however, toxicity has been reported and dosage adjustment in these cases may be warranted.

### 4.3 Contraindications

Patients with known hypersensitivity to Erythromycin.

Erythromycin is contraindicated with either astemizole or terfenadine.

Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), have been reported with the intravenous administration of erythromycin. Limited data suggest that these adverse effects may be associated with abnormally elevated serum erythromycin concentrations following rapid administration. Erythromycin therefore must not be administered rapidly by direct intravenous injection (IV push).

### 4.4 Special warnings and precautions for use

Allergic reactions ranging from urticaria to anaphylaxis have been reported with intravenous erythromycin.

Superinfection may occur with prolonged use, giving rise to overgrowth of non susceptible organisms.

Erythromycin is excreted principally via the liver and caution should be exercised when using erythromycin in patients with a degree of hepatic impairment or concomitantly receiving potentially hepatotoxic agents.

Extravasation should be avoided. The infusion should be slow to avoid pain along the vein.

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

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 carefully considered against the potential risk of developing IHPS. Patients should be informed to contact their physician if vomiting or irritability occurs.

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

**Penicillin:** Erythromycin, in low bacteriostatic concentrations, may inhibit the actions of bactericidal drugs. In high concentrations, erythromycin may act synergistically with penicillin.

Use of erythromycin in patients receiving digoxin, warfarin, carbamazepine or high doses of theophylline may result in potentiation of the effects due to impairment of excretion. Additionally a report has been noted on the potentiation of vinblastine with concomitant erythromycin therapy.

Increased plasma levels of cyclosporin may occur in patients on erythromycin.

Ergotism has been reported in patients receiving erythromycin in combination with ergot.

Concomitant use of erythromycin with terfenadine or astemizole is likely to result in an enhanced risk of cardiotoxicity with these drugs. The concomitant use of erythromycin with either astemizole or terfenadine is therefore contraindicated.

#### **4.6 Pregnancy and lactation**

##### Use in Pregnancy and Lactation

Erythromycin should not be administered to pregnant women unless the benefits outweigh the potential risks. Erythromycin crosses the placenta and gives rise to foetal plasma levels which are approximately 5-20 % of maternal limits. However the risks associated with this phenomenon have not been clearly established.

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.

#### **4.7 Effects on ability to drive and use machines**

Not applicable.

#### **4.8 Undesirable effects**

Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal) including atypical ventricular tachycardia (torsades de pointes), have been reported with the intravenous administration of erythromycin. Limited data suggest that these adverse effects may be associated with abnormally elevated serum erythromycin concentrations following rapid administration.

**Auditory/Vestibular:** In very high doses, erythromycin may cause transient perceptive deafness. Cases of Infantile Hypertrophic Pyloric Stenosis (IHPS) occurring in infants following erythromycin therapy have been reported (*see section 4.4, Special warnings and precautions for use*). Such infants present with vomiting or irritability with feeding.

## 4.9 Overdose

The toxicity is low. Overdosage may be associated with ototoxicity. No specific treatment has been proposed other than general supportive measures.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Erythromycin binds to the ribosomes of bacteria and affects protein synthesis without affecting nucleic acid 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 aminocyl transfer RNA and inhibiting polypeptide synthesis without causing any alteration in the nucleic acid cycle.

### 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.

#### Metabolism:

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

#### Excretion:

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.

#### Half-Life:

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

None.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium hydroxide (for pH-adjustment)  
Lactobionic acid solution (for pH-adjustment)

### 6.2 Incompatibilities

Erythromycin should not be reconstituted with inorganic salt solutions. Use only water for injections.

The stability of solutions of erythromycin lactobionate is adversely affected below pH 5.5. 5 ml of sterile 8.4% sodium bicarbonate solution will neutralise 1 litre of Glucose Injection BP and should be added to the bag prior to the addition of erythromycin lactobionate.

### 6.3 Shelf Life

As packaged for sale – 2 years

After reconstitution with sterile water for injections, chemical and physical in-use stability has been demonstrated for 72 hours at 2°C to 8°C.

After further dilution with 0.9% sodium chloride, chemical and physical in-use stability has been demonstrated for 72 hours at 2°C to 8°C. Or after further dilution with 5% w/v buffered glucose solution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. (*See section 6.6, Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product, for information on reconstitution and dilution methods*)

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 should not be longer than 24 hours at a temperature not exceeding 2°C to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

Contains no preservative. For single use. Discard any unused contents.

### 6.4 Special precautions for storage

As packaged for sale – Do not store above 25°C. Keep vial in the outer carton.

After reconstitution/dilution see section 6.3, *Shelf life*

### 6.5 Nature and contents of container

30 ml clear Type I glass vials in singles and packs of 10 vials.

## **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

Erythromycin lactobionate vials labeled as containing 1 gram of erythromycin should be initially reconstituted by adding 20 ml of Sterile Water for Injections BP without preservative, to provide a solution containing 50 mg per ml. No other diluent should be used to prepare this initial solution. It is important to ensure that the product is completely dissolved by vigorous shaking before transferring to infusion containers.

Prior to administration the concentrated solution must be further diluted in glass or flexible plastic containers of 0.9% sodium chloride injection. If, for clinical reasons, 0.9% saline is not suitable, then neutralised Glucose Intravenous Infusion BP 5% w/v may be used. Neutralised glucose solution is prepared by the addition of 5 ml of sterile 8.4% w/v sodium bicarbonate solution to each litre of Glucose Intravenous Injection BP 5% w/v.

It is necessary to buffer the glucose solution in this way because the stability of erythromycin lactobionate is adversely affected below pH 5.5.

Subsequent dilution into infusion fluids should be made prior to administration. Recommended fluids are Sodium Chloride Injection BP 0.9 % or Glucose 5 % Injection BP.

It is recommended that a clarifying filter is used to minimise the particulate levels in resultant infusions.

## **7 MARKETING AUTHORISATION HOLDER**

Hospira UK Limited  
Queensway  
Royal Leamington Spa  
Warwickshire CV31 3RW  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA 0437/025/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 17 April 1992

Date of last renewal: 17 April 2007

## **10 DATE OF REVISION OF THE TEXT**

February 2008