**SUMMARY OF PRODUCT CHARACTERISTICS**

1. **NAME OF THE MEDICINAL PRODUCT**

<TRADE NAME> <STRENGTH> Gastro-resistant Tablets

<REGARDING THE APPROVAL>

1. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains <GENERIC NAME> <STRENGTH>

<REGARDING THE APPROVAL>

For a full list of excipients, see section 6.1.

1. **PHARMACEUTICAL FORM**

Gastro-resistant tablets

<REGARDING THE APPROVAL>

1. **CLINICAL PARTICULARS**
	1. **Therapeutic indications**

For the prophylaxis and treatment of infections caused by Erythromycin sensitive organisms. <GENERIC NAME> has been shown to have in-vitro activity against the following microorganisms:

* Gram positive cocci: Staphylococci and Streptococci.
* Haemophilus influenzae, L-forms, Neisseria, Mycoplasma pneumoniae
* Legionella pneumophila, Branhamella catarrhalis, Bordetella pertussis
* Corynebacterium diphtheriae (as an adjunct to antitoxin)
* Treponema pallidum, Chlamydia trachomatis, Ureaplasma urealytica Clostridia, Campylobacter.

Clinical infections:

* *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 infections:* Otitis media and otitis externa, mastoiditis.
* *Eye infections:* Blepharitis
* *Oral/dental infections:* Gingivitis, Vincent's angina
* *Skin and soft tissue infections:* Boils and carbuncles, paronychia, bscesses, pustular acne, impetigo, cellulitis, erysipelas
* *Gastro-intestinal infections:* cholecystitis, staphylococcal enterocolitis
* *Prophylaxis:* pre- and post- operative trauma, burns, rheumatic fever
* *Other infections:* osteomyelitis, urethritis, gonorrhoea, syphilis, lymphogranuloma venereum, diphtheria, prostatitis, scarlet fever

Note: <GENERIC NAME> has also proved to be of value in endocarditis and septicaemia, but in these conditions initial administration of <GENERIC NAME> lactobionate by the intravenous route is advisable.

* 1. **Posology and method of administration**

*Posology*

Adults and children over 8 years:

For mild to moderate infections 2g daily in divided doses Up to 4g daily in severe infections.

Paediatric population: Age, weight and severity of the infection are important factors in determining the correct dosage.

Note: For younger children, infants and babies, Erythroped, <GENERIC NAME> ethylsuccinate suspensions, are normally recommended. The recommended dose for children age 2-8 years, for mild to moderate infections, is 1 gram daily in divided doses. The recommended dose for infants and babies, for mild to moderate infections, is 500 mg daily in divided doses. For severe infections doses may be doubled.

Elderly: No special dosage recommendations.

*Method of administration:*

For Oral administration

### Contraindications

* Hypersensitivity to the active substance(s) or any of the excipients listed in section 6.1
* Patients taking simvastatin, tolterodine, mizolastine, amisulpride, astemizole, terfenadine, domperidone, cisapride or pimozide.
* <GENERIC NAME> is contraindicated with ergotamine and dihydroergotamine
* <GENERIC NAME> 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)
* <GENERIC NAME> should not be given to patients with electrolyte disturbances (hypokalaemia, hypomagnesaemia due to the risk of prolongation of QT interval)

### Special warnings and precautions for use

### Cardiovascular Events

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

Carefully consider the balance of benefits and risks before prescribing <GENERIC NAME> 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).

<GENERIC NAME> 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 <GENERIC NAME>.

Caution should be exercised in administering this antibiotic to patients with renal impairment and patients with a predisposition to QT interval prolongation. This product should not be used in patients with porphyria.

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) 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.

Care should be taken when administering this product to patients who are pregnant or breastfeeding. 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.

Pseudomembranous colitis has been reported with nearly with all antibacterial agents, including macrolides, and may range in severity from mild to lifethreatening (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 broad spectrum antibiotics, pseudomembranous colitis has been reported rarely with erythromycin.

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. 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.

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.

This medicine contains less than 1mmol sodium (23mg) per tablet, which is to say essentially ‘sodium free’

#### 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, antifungals e.g fluconazole, ketoconazole and itraconazole and warfarin. 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. Erythromycin has also been reported to potentiate the effects of corticosteroids.

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.

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.

The metabolism of terfenadine, pimozide and astemizole is significantly altered when either are taken concomitantly with erythromycin. Rare cases of serious potentially fatal cardio-vascular events have been observed, including torsades de pointes, other ventricular arrhythmias and cardiac arrest. Death has been reported with the terfenadine/erythromycin combination (see sections 4.3 and 4.8).

Concomitant use of erythromycin with simvastatin, tolterodine, mizolastine, amisulpride, terfenadine or astemizole is likely to result in an enhanced risk of cardio toxicity with these drugs. The concomitant use of erythromycin with either simvastatin, tolterodine, mizolastine, amisulpride, astemizole or terfenadine is therefore contraindicated.

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.

Post-marketing reports indicate that concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity, characterised by the rapid development of severe peripheral vasospasm, dysaesthesia 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. The 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.

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.

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 also been reported to potentiate the effect of corticosteroids.

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

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

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, therefore, caution should be exercised when erythromycin is administered to lactating mothers, due to reports of infantile hypertrophic pylori stenosis in breast-fed infants.

Fertility

Animal studies have shown no hazard.

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

#### Erythromycin 250mg Gastro-resistant Tablets has no influence on the ability to drive and use machines.

#### Undesirable effects

#### Blood and lymphatic system disorders:

#### Eosinophilia.

#### Cardiac disorders SOC

#### QTc interval prolongation, torsades de pointes, palpitations, and cardiac rhythm disorders including ventricular tachyarrhythmias. Cardiac arrest, ventricular fibrillation (frequency not known).

#### Ear and labyrinth disorders

#### Deafness, tinnitus There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency or high doses.

#### Eye disorders

#### Mitochondrial Optic Neuropathy

#### Gastrointestinal disorders

#### The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. The following have been reported: upper abdominal discomfort, nausea, vomiting, diarrhoea, pancreatitis, anorexia, infantile hypertrophic pyloric stenosis.

#### Pseudomembranous colitis has been rarely reported in association with erythromycin therapy (see section 4.4).

#### General disorders and administration site conditions

#### Chest pain, fever, malaise.

#### Hepatobiliary disorders

#### Cholestatic hepatitis, jaundice, hepatic disfunction, hepatomegaly, hepatic failure, hepatocellular hepatitis (see section 4.4).

#### Immune system disorders

#### Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

#### Investigations

#### Increased liver enzyme values.

## Nervous system disorders

## 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.

## Psychiatric disorders

## Hallucinations

## Renal and urinary disorders

## Interstitial nephritis

## Skin and subcutaneous tissue disorders

## Skin eruptions, pruritus, urticaria, exanthema, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.Not known: acute generalised exanthematous pustulosis (AGEP)

## Vascular disorders

## Hypotension.

## 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 Health Product Vigilance Center; HPVC

### Overdose

### Symptoms: hearing loss, severe nausea, vomiting and diarrhoea.

### Treatment: gastric lavage, general supportive measures.

# PHARMACOLOGICAL PROPERTIES

# Pharmacodynamic properties

# Pharmacotherapeutic Group: Macrolides

# ATC Code: J01FA01

# 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, Lforms, the agents causing trachoma and lymphogranuloma venereum

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

### Pharmacokinetic properties

### Absorption and Fate

### Peak blood levels normally occur within one hour of dosing of erythromycin ethylsuccinate granules. The elimination half life is approximately two hours. Dose may be administered two, three or four times a day. Erythromycin is adversely affected by gastric acid. For this reason erythromycin tablets are enteric coated.

### It is absorbed from the small intestine. It is widely distributed throughout body tissues. Little metabolism occurs and only about 5% is eliminated in the urine. It is excreted principally by the liver.

### t max = 4h

### C max = 0.3 – 0.5 ug/ml

### Vd = 0.78 + 0.44 1/kg

### T 1/2 = 1.6 +/- 0.7h

### CLEARANCE = 9.1 – 4.1 ml/min/kg

### 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

### PHARMACEUTICAL PARTICULARS

### List of excipients

### <REGARDING THE APPROVAL>

* 1. **Incompatibilities**

<REGARDING THE APPROVAL>

* 1. **Shelf life**

<REGARDING THE APPROVAL>

* 1. **Special precautions for storage**

<REGARDING THE APPROVAL>

* 1. **Nature and contents of container**

<REGARDING THE APPROVAL>

 **6.6.Special precautions for disposal**

<REGARDING THE APPROVAL>

1. **MARKETING AUTHORISATION HOLDER**

<REGARDING THE APPROVAL>

1. **MARKETING AUTHORISATION NUMBER(S)**

<REGARDING THE APPROVAL>

1. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<REGARDING THE APPROVAL>

1. **DATE OF REVISION OF THE TEXT[[1]](#footnote-1)**

<REGARDING THE APPROVAL>

1. Ref: Erythromycin, MHRA, 30/03/2022 [↑](#footnote-ref-1)