Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Erythromycin 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg erythromycin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets
White tablets embossed with the letter ‘T’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Erythromycin 250 mg Tablets are indicated in adults and children aged over 8 years for the treatment of infections caused by erythromycin-sensitive organisms. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults and children over 8 years.
For mild to moderate infections 1 to 2 g daily in divided doses. Up to 4 g daily in severe infections.

Elderly:
No special dosage recommendations.

Paediatric population
Erythromycin 250 mg Tablets are not recommended for use in children aged under 8 years. For younger children, infants and babies, Erythroped, erythromycin ethylsuccinate suspensions, are normally recommended.

Hepatic impairment
Erythromycin should be used with caution in patients with impaired hepatic function (see sections 4.4 & 5.2).

Method of administration
For oral administration

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Erythromycin is contraindicated in patients taking astemizole, terfenadine, domperidone, cisapride or pimozide. Erythromycin is contraindicated with ergotamine and dihydroergotamine. Erythromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.4, 4.5 and 4.8).

4.4 Special warnings and precautions for use

Erythromycin is excreted principally by the liver, so caution should be exercised in administering the antibiotic to patients with impaired hepatic function or concomitantly receiving potentially hepatotoxic agents. Hepatic dysfunction including increased liver enzymes and hepatocellular 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 is a risk of developing visual impairments after exposure to erythromycin. For some patients, a pre-existing dysfunction in mitochondrial metabolism from genetic causes such as Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) might play a contributing role.

HMG-CoA Reductase Inhibitors: Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (statins). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Erythromycin is contraindicated in patients receiving the HmG-CoA reductase inhibitors lovastatin and simvastatin (see section 4.3 and 4.5). If treatment with erythromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

In situations where the concomitant use of erythromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

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.

Prolonged or repeated use of erythromycin may result in overgrowth of non- susceptible bacteria or fungi. If super-infection occurs, erythromycin should be discontinued and appropriate therapy instituted.

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.

QT Prolongation
Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during post marketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval (see section 4.8).

Patients receiving erythromycin concurrently with drugs which can cause prolongation of the QT interval should be carefully monitored. The concomitant use of erythromycin with some of these drugs is contraindicated (See sections 4.3 & 4.5)

Laboratory Tests
Erythromycin interferes with the fluorometric determination of urinary catecholamines.

4.5 Interaction with other medicinal products and other forms of interaction

Erythromycin is a moderate inhibitor of CYP3A4 mediated metabolism and P- glycoprotein.

Increases in serum concentrations of the following drugs metabolised by the cytochrome P450 system may occur when administered concurrently with erythromycin: acenocoumarol, alfentanil, astemizole, bromocriptine, carbamazepine, cilostazol, cyclosporin, digoxin, dihydroergotamine, disopyramide, ergotamine, hexobarbitone, methylprednisolone, midazolam, omeprazole, phenytoin, quinidine, rifabutin, sildenafil, tacrolimus, terfenadine, domperidone, theophylline, triazolam, valproate, vinblastine, and antifungals e.g. fluconazole, ketoconazole and itraconazole. Appropriate monitoring should be undertaken and dosage should be adjusted as necessary. Serum concentrations of drugs metabolised by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin. The prescriber should consult appropriate reference sources for additional information. 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 is contraindicated in patients receiving the HmG-CoA reductase inhibitors lovastatin and simvastatin (see section 4.3). Erythromycin has been reported to increase concentrations of HMG- CoA reductase inhibitors. 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 H_1 antagonists: care should be taken in the co-administration of erythromycin with H_1 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, torsades de pointes, and other ventricular arrhythmias have been observed (see section 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 characterized 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.

There have been reports that maternal macrolide antibiotics exposure within 10 weeks of delivery may be associated with a higher risk of infantile hypertrophic pyloric stenosis (IHPS).
Erythromycin should be used by women during pregnancy only if clearly needed.

Breast-feeding
Erythromycin is excreted in breast milk, therefore, caution should be exercised when erythromycin is administered to a nursing mother. There has been report of a breast-fed infant who developed pyloric stenosis thought to be associated with use of erythromycin by the mother. Erythromycin is concentrated in human breast milk and adverse effects have been seen in breast-fed infants whose mothers were receiving erythromycin and therefore it is to be used with caution in nursing mothers.

A cohort study concluded that the use of macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin, or spiramycin) during breast-feeding increased the risk of infantile hypertrophic pyloric stenosis (see Section 4.4)

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse drug effects reported with erythromycin originate from multiple sources, including spontaneous reports and frequency cannot be estimated from the available data.

System organ class	**Adverse reactions**
Blood and lymphatic system disorders	Eosinophilia.
Immune system disorders	Hypersensitivity, anaphylactic reaction.
Psychiatric disorders	Hallucination.
Nervous system disorders	Dizziness. There have been isolated reports of transient central nervous system side effects including confusional state, convulsions, and vertigo; however, a cause and effect relationship has not been established.
Eye Disorders	Visual impairment (see section 4.4).
Ear and labyrinth disorders	Deafness, tinnitus, vertigo. There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency or taking high doses.
Cardiac disorders	QTc interval prolongation, torsades de pointes, palpitations, and cardiac rhythm disorders including ventricular tachyarrhythmias.
Vascular disorders	Hypotension.
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).
Hepatobiliary disorders	Cholestatic hepatitis, jaundice, abnormal hepatic function, hepatomegaly, hepatic failure, hepatitis (see section 4.4).

Skin and subcutaneous tissue disorders	Rash, pruritus, urticaria, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.
Musculoskeletal and connective tissue disorders	Rhabdomyolysis (see sections 4.3, 4.4 and 4.5).
Renal and urinary disorders	Tubulointerstitial nephritis
General disorders and administration site conditions	Chest pain, pyrexia, malaise.
Investigations	Increased hepatic enzymes.

Reporting of suspected adverse reactions
Reporting of 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
hearing loss, severe nausea, vomiting and diarrhoea.

Management
gastric lavage, general supportive measures.

In case of overdosage, erythromycin should be discontinued. Erythromycin is not removed by peritoneal dialysis or haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Macrolides
ATC Code: J01FA

Mechanism of action
Erythromycin exerts its antimicrobial action by binding to the 50 S ribosomal sub- unit of susceptible microorganisms and suppresses protein synthesis. Biochemical tests demonstrate erythromycin inhibits protein synthesis of the pathogen without directly affecting nucleic acid synthesis. Antagonism has been demonstrated between clindamycin and erythromycin, lincomycin and chloramphenicol.

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

Gram positive bacteria - *Listeria monocytogenes, Corynebacterium diphtheriae* (as an adjunct to antitoxin), *Staphylococci* spp, *Streptococci* spp (including *Enterococci).*

Gram negative bacteria - *Haemophilus influenzae, Neisseria meningitidis, Neisseria gonorrhoeae, Legionella pneumophila, Moraxella (Branhamella) catarrhalis, Bordetella pertussis, Campylobacter* spp.

Mycoplasma - *Mycoplasma pneumoniae, Ureaplasma urealyticum.*

Other organisms - *Treponema pallidum, Chlamydia* spp, *Clostridia* spp, L-forms, the agents causing trachoma and lymphogranuloma venereum.

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

5.2 Pharmacokinetic properties

Absorption

Peak blood levels normally occur within one hour of dosing of erythromycin ethylsuccinate granules. The elimination half life is approximately two hours. Doses may be administered two, three or four times a day.

Erythromycin ethylsuccinate is less susceptible than erythromycin to the adverse effect of gastric acid. It is absorbed from the small intestine.

Distribution

It is widely distributed throughout body tissues. Only low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis.

Elimination

In patients with normal hepatic function, erythromycin is concentrated in the liver and excreted via the bile. The effect of hepatic dysfunction on excretion of erythromycin by liver into the bile is not known. Little metabolism occurs and only about 5% is excreted in the urine.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term (2 years) oral studies conducted in rats up to about 400 mg/kg/day and in mice up to about 500 mg/kg/day with erythromycin base did not provide evidence of tumorigenicity. Mutagenicity studies conducted did not show any genotoxic potential, and there was no apparent effect on male or female fertility in rats treated with erythromycin base by oral gavage at 700 mg/kg/day.
There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed dosed by oral gavage at 350 mg/kg/day (7 times the human dose) of erythromycin base prior to and during mating, during gestation and through weaning.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if it is clearly needed.
Erythromycin has been reported to cross the placental barrier in humans, but foetal plasma levels are generally low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Carmellose Sodium
Cellulose microcrystalline
Povidone
Polacrilin Potassium
Talc
Magnesium Stearate

Sub Coat
Hypromellose
Hydroxypropylcellulose
Propylene Glycol
Sorbitan Oleate

Gastro-resistant Coat
Methacrylic Acid – Ethyl Acrylate Copolymer
Talc
Titanium Dioxide
Triethyl Citrate
Antifoam Emulsion

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original container in order to protect from light.

6.5 Nature and contents of container

Type III amber glass bottles with a urea outer/aluminium liner cap, of 100 tablets.

Polypropylene bottles with either an LDPE or an HDPE closure, of 50, 100, 500 and 1000 tablets.

Aluminium foil/clear or opaque PVC/PVDC blisters in packs of 28, 40 and 56 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
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8 MARKETING AUTHORISATION NUMBER

PA1142/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 01 November 2007

10 DATE OF REVISION OF THE TEXT

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