

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Erythromycin Tablets 250mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Erythromycin 250 mg

Excipient(s) with known effect

Also contains lactose and colourant E124.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Red enteric film coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the prophylaxis and treatment of infections caused by erythromycin-sensitive organisms.

Erythromycin is highly effective in the treatment of a great variety of clinical infections such as:

1. Upper respiratory tract infections: tonsillitis, peritonsillar abscess, pharyngitis, laryngitis, sinusitis, Bordetella Pertussis infection, secondary infections in influenza and common colds
2. Lower respiratory tract infections: tracheitis, acute and chronic bronchitis, pneumonia (lobar pneumonia, bronchopneumonia, primary atypical pneumonia), bronchiectasis, Legionnaire's disease
3. Ear infection: otitis media and otitis externa, mastoiditis
4. Oral infections: gingivitis, Vincent's angina
5. Eye infections: blepharitis

6. Skin and soft tissue infections: boils and carbuncles, paronychia, abscesses, pustular acne, impetigo, cellulitis, erysipelas
 7. Gastrointestinal infections: cholecystitis, staphylococcal enterocolitis, campylobacter enteritis
 8. Prophylaxis: pre- and post- operative trauma, burns, rheumatic fever, bacterial endocarditis in patients allergic to penicillin with congenital heart disease, or rheumatic or other acquired valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract.
 9. Other infections: urethritis, diphtheria, prostatitis and scarlet fever.
10. Bone infections: osteomyelitis
 11. Sexually transmitted diseases: gonorrhoea, syphilis, lymphogranuloma venereum

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

4.2 Posology and method of administration

Posology

Adults and children over 8 years:

1-2 g daily in divided doses for mild to moderate infection

For severe infections this dosage may be increased to up to 4 g daily in divided doses. Erythromycin tablets should be taken when fasting or immediately before food.

Elderly:

No special dosage recommendations.

Children under 8 years:

An Erythromycin suspension is recommended. *Period of dosing with regard to indications:* Upper respiratory tract infections: 5 to 10 days

Lower respiratory tract infections: 7 to 14 days or until the signs and symptoms indicate that the condition is cured. Legionnaire's Disease requires prolonged treatment. It is recommended that initially Erythromycin lactobionate intravenously should be administered.

Skin and soft tissue infections: 5 to 10 days. Acne may require prolonged treatment.

Sexually transmitted diseases - NGU and syphilis: 10 to 21 days. Some conditions may require prolonged treatment.

Oral and dental infections: at least 5 days.

Eye infections - Chlamydia inclusion conjunctivitis: 3 weeks. Gastro-intestinal infections - Campylobacter: a minimum of 5 days. Erythromycin is taken by mouth.

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 simvastatin, tolterodine, mizolastine, amisulpride, astemizole, terfenadine, domperidone, cisapride or pimozone.

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).

Erythromycin is contraindicated with ergotamine and dihydroergotamine.

Concomitant administration of erythromycin and lomitapide is contraindicated (see section 4.5).

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/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.

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.

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.

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.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with statins.

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).

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.

Erythromycin tablets contain the colour red E124 which may cause allergic reactions.

Erythromycin tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Increases in serum concentrations of the following drugs metabolised by the cytochrome P450 system may occur when administered concurrently with erythromycin: acenocoumarol, alfentanil, astemizole, bromocriptine, carbamazepine, cilostazol, cyclosporin, digoxin, dihydroergotamine, disopyramide, ergotamine, hexobarbitone, methylprednisolone, midazolam, omeprazole, phenytoin, quinidine, rifabutin, sildenafil, tacrolimus, terfenadine, domperidone, theophylline, triazolam, valproate, vinblastine, and antifungals e.g. fluconazole, ketoconazole and itraconazole. Appropriate monitoring should be undertaken and dosage should be adjusted accordingly. 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.

Corticosteroids

Caution should be exercised in concomitant use of erythromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

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.

Concomitant administration of erythromycin with lomitapide is contraindicated due the potential for markedly increased transaminases (see section 4.3).

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.

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 sections 4.3 and 4.8).

Anti-bacterial agents: an *in vitro* antagonism exists between erythromycin and the bactericidal beta-lactam antibiotics (e.g. penicillin, cephalosporin). Erythromycin antagonises the action of clindamycin, lincomycin and chloramphenicol. The same applies for streptomycin, tetracyclines and colistin.

Protease inhibitors: in concomitant administration of erythromycin and protease inhibitors, an inhibition of the decomposition of erythromycin has been observed.

Oral anticoagulants: there have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants (e.g. warfarin, 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 co-administration of erythromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm and ischaemia of the central nervous system, extremities and other tissues (see section 4.3).

Hydroxychloroquine and chloroquine: Erythromycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events. 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.

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

The available epidemiological studies on the risk of major congenital malformations with use of macrolides including erythromycin during pregnancy provide conflicting results. Some 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).

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.

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.

Breast-feeding

Erythromycin can be excreted into breast milk. Caution should be exercised when administering erythromycin to lactating mothers due reports of infantile hypertrophic pyloric stenosis in breast-fed infants.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

The following undesired events, listed by body system, have been reported with erythromycin:

Blood and lymphatic system disorders:

Eosinophilia

Cardiac disorders:

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.

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 with erythromycin therapy (see section 4.4).

General disorders and administration site conditions:

Chest pain, fever, malaise.

Hepatobiliary disorders:

Cholestatic hepatitis, jaundice, hepatic dysfunction 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.

Eye disorders:

Mitochondrial optic neuropathy.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple APP Store.

4.9 Overdose

Symptoms

Hearing loss, severe nausea, vomiting and diarrhoea.

Management

Gastric lavage, general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectives for Systemic Use, Macrolides, ATC code: J01FA01.

Erythromycin exerts its antimicrobial action by binding to the 50S ribosomal subunit 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, 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

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. It is widely distributed throughout body tissues. Little metabolism occurs and only about 5% is excreted in the urine. It is excreted principally by the liver.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core excipients:

Lactose

Maize starch

Potato starch

Sodium starch glycollate

Magnesium stearate

Coat excipients:

Cellulose Acetate Phthalate

Diethyl phthalate

Al Lake (E124)

Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Containers: 36 months

PVC/PVDC/Aluminium Blister packs: 36 months

PVC/Aluminium Blister packs: 48 months

6.4 Special precautions for storage

Do not store above 25°C.

Containers: Store in the original container and keep the container tightly closed.

Blister packs: Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container

High density polyethylene or polypropylene containers with polythene or polypropylene lids and polyurethane/polythene inserts.

PVC/Aluminium or PVC/PVDC/Aluminium blister packs.

Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 42976/0005

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