SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Erythromycin 500mg Tablets

2 Qualitative and Quantitative composition

Each tablet contains erythromycin stearate equivalent to erythromycin BP 500mg.

Excipient with known effect:
Tartrazine (E102) 3.90mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Erythromycin is effective in the treatment of a great variety a clinical infections.

1. Upper respiratory tract infection: Tonsillitis, peritonsillar abscess, pharyngitis, laryngitis, sinusitis, secondary infections in clods and influenza.
2. Lower respiratory tract infections: Tracheitis, acute and chronic bronchitis, pneumonia, bronchiectasis.
3. Oral infections: Gingivitis, Vincent's angina.
4. Eye infections: Blepharitis.
5. Ear infections: otitis media and otitis externa, mastoiditis.
6. Skin and soft tissue infections: boils and carbuncles, paronychia, abscesses, acne, impetigo, cellulitis, erysipelas.
7. Prophylazis: pre- and post-operative, trauma, burns, rheumatic fever.

8. Genito-urinary infections: Urethritis, gonorrhoea, syphilis, lymphogranuloma venereum, prostatitis.
9. Other infections: Osteomyelitis, diphtheria, scarlet fever.

Microbiological indications:

Erythromycin is active against a wide range of gram-positive staphylococci, pneumococci and streptococci, Meningococci, *Mycoplasma*, L-forms, *Haemophilus influenzae*, agents causing trachoma and lymphogranuloma vernereum, *Chlamydia*, clostridia, coryneacteria, *Neisseria*, *Treponema pallidum* and *Bordetella*.

4.2 Posology and method of administration

Adults:

1g to 2g/day erythromycin activity divided into 6, 8 or 12 hourly doses. May be increased to up to 4g daily in divided doses in severe infections. Tablets should be taken before and with meals.

Children:

Normally use Erythromycin Suspension. If tablets are used calculate dose on basis of 30mg erythromycin activity/kg/day in divided doses. In severe infections this may be raised to 50mg/kg/day in divided doses.

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 pimozide. 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.

This product should not be used in patients with porphyria.

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.

Patients received 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 in contraindicated (see sections 4.3 and 4.5)

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.

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.

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.

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).

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, antifungals e.g fluconazole, ketoconazole and itraconazole. 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.

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 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.

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

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 contra-indicated.

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, torsade 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.

Corticosteroids: Caution should be exercised in concomitant use of erythromycin with systemic and inhaled corticosteroids that are primarily metabolized 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.

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.

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

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).

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

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

Erythromycin is excreted in breast milk, therefore, caution should be exercised when administering erythromycin to lactating mothers due to reports of infantile hypertrophic pyloric stenosis in breast-fed infants.

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.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable Effects

Blood and lymphatic system disorders:

Eosinophilia.

Cardiac disorders

QTc interval prolongation, torsades de pointes, palpitations, and cardiac rhythm disorders including ventricular tachyarrhythmias.

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 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 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 (frequency cannot be estimated from the available data): acute generalised exanthematous pustulosis (AGEP)

Vascular disorders

Hypotension.

The rare possibility of super infection caused by overgrowth of non-susceptible bacteria or fungi should be considered during prolonged or repeated therapy, especially when other antibacterial agents are simultaneously employed.

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.

Treatment: Gastric lavage, general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 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, 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.
Erythromycin ethylsuccinate is less susceptible than erythromycin to the adverse effect of gastric acid. It is absorbed from the small intestine. For this reason erythromycin tablets are enteric coated.

Distribution

It is widely distributed throughout the body tissues.

Elimination

The elimination half-life is approximately two hours. Doses may be administered two, three or four times a day. Little metabolism occurs and only about 5% is excreted in the urine. It is excreted principally by the liver.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone

Magnesium stearate
Maize starch
Sodium citrate
Amberlite
Microcrystalline cellulose
Cellulose acetate phthalate
Polyethylene glycol 6000
Castor oil
Triacetin
Talc
Tartrazine (E102)
Erythrosine (E127)

6.2 Incompatibilities

Not known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool dry place.

6.5 Nature and contents of container

Securitainers

Pack size: 100

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Ennogen Pharma Limited
Unit G4,
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Riverside Way,
Dartford,
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8 MARKETING AUTHORISATION NUMBER(S)

PL 40147/0035

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12/09/2023