PHARMACEUTICALS LIMITED

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) OF

THROMYCIN® (ERYTHROMYCIN 125MG/5ML) SUSPENSION

1. NAME OF THE MEDICINAL PRODUCT

Thromycin® (Erythromycin 125mg/5ml) Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of the suspension contains Erythromycin 125mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Suspension

4. Clinical particulars

4.1 Therapeutic indications

Thromycin® Suspension is indicated for the relief of a wide variety of bacterial infections. It may also be used to prevent certain bacterial infections. Erythromycin is known as a macrolide antibiotic. It works by stopping the growth of bacteria. This antibiotic treats or prevents only bacterial infections.

Erythromycin is an antibiotic used for the treatment of a number of bacterial infections. This includes respiratory tract infections, skin infections, chlamydia infections, pelvic inflammatory disease, and syphilis. It may also be used during pregnancy to prevent Group B streptococcal infection in the newborn, as well as to improve delayed stomach emptying. It can be given intravenously and by mouth. An eye ointment is routinely recommended after delivery to prevent eye infections in the newborn.

Posology and method of administration

Posology

Important Dosage and Administration Instructions

Paediatric population

Age, weight, and severity of the infection are important factors in determining the proper dosage. In mild to moderate infections the usual dosage of Erythromycin for children is 30 to 50 mg/kg/day in equally divided doses every 6 hours.

Children up to 2 years: 30mg/kg/day in divided doses. For severe infections up to 50mg/ kg/ day in divided doses.

Children 2-8 years: 30 mg/kg/day in divided doses. For severe infections up to 50 mg/ kg/ day in divided doses.

Adults and children over 8 years: 2g/day in divided doses. For severe infections up to 4g/ day in divided doses.

Normal dose: 250mg four times a day or 500mg twice daily.

Normal dose: 125mg four times a day or 250mg twice daily.

Presentations are available for adults and children over 8 years, children aged 2-8 years, and for children under 2 years.

Hepatic impairment

Erythromycin should be used with caution in patients with impaired hepatic function. Hepatic function should be monitored in patients receiving prolonged treatment with erythromycin

Renal impairment

No dosage adjustment needed.

Elderly

No dosage adjustments are required in the elderly.

Method of administration

Erythromycin Ethylsuccinate suspension: It may be given without regard to meals; however, studies have shown better absorption when given with milk or food.
Shake well before administration. Administer using a calibrated measuring device.

4.2 Contraindications

Erythromycin is contraindicated in patients who have the following:

- diarrhea from an infection with Clostridium difficile bacteria
- myasthenia gravis, a skeletal muscle disorder
- hearing loss
- torsades de pointes, a type of abnormal heart rhythm
- prolonged QT interval on EKG
- abnormal EKG with QT changes from birth
- liver problems
- abnormal liver function tests
- inflammation of the liver with stoppage of bile flow

Erythromycin is contraindicated in patients taking simvastatin, tolterodine, mizolastine, amisulpride, astemizole, terfenadine, domperidone, cisapride or pimozide.
Erythromycin is contraindicated with ergotamine and dihydroergotamine.

4.3 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. 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.

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.

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 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.

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.

4.4 Interaction with other medicinal products and other forms of interaction

Clinically Significant Drug Interactions with Erythromycin Etylsuccinate

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. 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 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.

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.

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 characterised by vasospasm and ischaemia of the central nervous system, extremities and other tissues.

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.

Pregnancy and Lactation

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 pyloric stenosis (IHPS).
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.

4.5 Effects on ability to drive and use machines

None reported

4.6 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 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.

General disorders and administration site conditions

Chest pain, fever, malaise.

Hepatobiliary disorders

Cholestatic hepatitis, jaundice, hepatic disfunction, hepatomegaly, hepatic failure, hepatocellular hepatitis.

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, prurituls, 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.

4.7 Overdose

Symptoms: hearing loss, severe nausea, vomiting and diarrhoea.
Treatment: gastric lavage, general supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Peak blood levels normally occur within 1 hour of dosing of Erythromycin Ethylsuccinate granules. The elimination half-life is approximately 2 hours. Doses may be administered 2, 3 or 4 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

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

Vanilla powder
Aerosil 200
Sodium Benzoate
Sodium Citrate

Citric Acid
Sucrose
Sodium Saccharin
Sodium CMC
Tartrazine Yellow
Corn starch

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 Months

6.4 Special precautions for storage

None

6.5 Nature and contents of container and special equipment for use, administration orimplantation

Thromycin® Suspension is presented as a light yellow granules contained in Thromycin powder for oral suspension labelled 100ml bottle with white ropp cap packed in a cardboard carton with leaflet enclosed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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