PRODUCT LITERATURE

EOMYCIN GRANULES 200MG/5ML
Each 5 ml contains:
Erythromycin Ethyl Succinate equivalent to Erythromycin 200 mg

Description
White granules which becomes pink suspension upon reconstitution.

Pharmacodynamics properties
Pharmacotherapeutic group: Macrolides, Lincosamides and Streptogramins, Macrolides

Mechanism of action
- 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 influenza, 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 influenza are susceptible to the concentrations reached after ordinary doses.

Pharmacokinetics properties
Absorption is facilitated if the stomach is empty. 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.

The drug is not removed by either peritoneal dialysis or haemodialysis. It diffuses readily into intracellular fluids and antibacterial activity can be achieved at essentially all sites. There is some retention on liver and spleen. Only low concentrations are achieved in cerebrospinal fluid, unless the meninges are inflamed. Diffusion into the aqueous humour, but not the vitreous humour of the eye is good. A significant proportion is bound to serum proteins.

Indication
For the treatment of infections caused by organisms susceptible to erythromycin.

Route of administration
Oral.

Recommended Dose
Adult: 400 mg every 6 hourly, up to 4 gm a day
Children: 30 - 50 mg/kg body weight per day.

Direction for mixing:
Shake container to loosen powder. Add about 30 ml water & shake well. Make up volume to 60 ml with water.

Contraindication
Hypersensitivity to the active substance or to any of the excipients.

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

Erythromycin is contraindicated with ergotamine and dihydroergotamine.

Warning and Precautions
- In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], EOMYCIN GRANULES 200MG/5ML should be discontinued immediately and appropriate treatment should be urgently initiated.

- 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 and caregivers should be informed to contact their physician if vomiting and/ 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.
- 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. 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.

Interactions with Other Medicament
- 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, 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

- 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 pyloric stenosis (IHPS).

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

Side Effects

- Skin and Subcutaneous Tissue Disorders
  - Frequency not known : severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP).

- Postmarketing Experience:
  - Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis.

- Blood and lymphatic system disorders
  - Eosinophilia.
- Immune system disorders
  - Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.
- Psychiatric disorders
  - Hallucinations
- 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.
- Eye disorders
  - Mitochondrial Optic Neuropathy
- Ear and labyrinth disorders
  - Deafness, tinnitus
  - 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
- Hepatobiliary disorders
  - Cholestatic hepatitis, jaundice, hepatic diysfunction, hepatomegaly, hepatic failure, hepatocellular hepatitis.
- 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).
- Renal and urinary disorders
  - Interstitial nephritis
- General disorders and administration site conditions
  - Chest pain, fever, malaise.
- Investigations
  - Increased liver enzyme values.

Symptoms and Treatment of Overdose
Symptoms: hearing loss, severe nausea, vomiting and diarrhoea.
Treatment: gastric lavage, general supportive measures.
Erythromycin is not dialysable.

Packing
Packed in plastic bottle of 60 ml.

Storage Conditions
Store below 30^{o}C, in a dry place, protected from direct light.

Keep away from reach of children.
Jauhkan daripada kanak- kanak

SHAKE WELL BEFORE USE

Expiry Date
2 years from date of manufacture

Name and Address of Product Registration Holder/ Manufacturer:
TERAPUTICS SDN. BHD. (590500-W)
Lot 10 & 11, PERDA Industrial Park,
Lorong IKS Simpang Ampat B,
14100 Simpang Ampat, S.P.S.,
Pulau Pinang, Malaysia

Name and Address of Distributor:
ZONTRON PHARMACEUTICALS SDN.BHD. (445695-T)
Lot 10 & 11, PERDA Industrial Park,
Lorong IKS Simpang Ampat B,
14100 Simpang Ampat, S.P.S.,
Pulau Pinang, Malaysia

Malaysian Drug Registration No. :
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