SM PHARMACEUTICALS SDN. BHD.

ELTHROCIN (ERYTHROMYCIN) TABLETS 250 MG AND 500 MG

DESCRIPTION:

250 mg: Red, round shaped, biconvex, scored, film coated tablets, with break line and 'SM' embossed on one side.
500 mg: Pink coloured, oval shaped, film-coated tablets, with break line on one side.

COMPOSITION:

Each tablet contains erythromycin stearate equivalent to 250 or 500 mg of erythromycin.

ACTIONS AND MODE OR MECHANISMS OF ACTION:

Erythromycin is a bacteriostatic macrolide antibiotic. However, it may be bactericidal in high concentrations or when used against highly susceptible organisms. It is thought to penetrate the bacterial cell membrane and to reversibly bind to the 50 S subunit of bacterial ribosomes; it does not directly inhibit peptide formation, but rather inhibits the translocation of peptides from the acceptor site on the ribosome to the donor site, inhibiting subsequent protein synthesis. Erythromycin is effective only against actively dividing organisms.
Erythromycin is a broad-spectrum antibiotic with activity against gram-positive and gram-negative bacteria, and other infectious agents, including *Chlamydia trachomatis, mycoplasmas (Mycoplasma pneumoniae* and *Ureaplasma urealyticum),* and spirochetes (*Treponema pallidum* and *Borrelia* species).
Erythromycin has good activity against *Streptococcus pneumoniae, S. pyogenes (group A beta-hemolytic streptococci), and Staphylococcus aureus.*
Many other Gram-positive organisms respond to erythromycin including *Bacillus anthracis, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae,* and *Listeria monocytogenes,* and it is usually moderately effective against the anaerobic *Clostridium* spp. *Nocardia* spp. vary in their susceptibility, but erythromycin is effective against *Propionibacterium acnes.*
Gram-negative cocci include *Neisseria meningitidis* and *N. gonorrhoeae,* and *Moraxella (Branhamella) catarrhalis.*
Erythromycin also has good activity against certain gram-negative bacteria, including *Legionella pneumophila, Helicobacter pyloridis, Campylobacter jejuni,* and *Bordetella pertussis, some Brucella strains, Flavobacterium,* and *Pasteurella. Haemophilus ducreyi* is reportedly susceptible, but *H. influenzae* is somewhat less so. Erythromycin is synergistic with sulphonamides against *Haemophilus influenza.*

PHARMACOLOGY (SUMMARY OF PHARMACODYNAMICS AND PHARMACOKINETICS):

Absorption:

Erythromycin stearate is acid-labile so is given in film-coated tablets. The stearate is hydrolysed in the intestine and the free erythromycin absorbed. Its absorption is delayed by food. High carbohydrate, fat and protein meals reduce the absorption of the stearate by 53 – 64%. Bioavailability varies between 30 and 65%, depending on the salt.

Distribution:

Erythromycin is widely distributed throughout body tissues and fluids. Only low concentrations are normally achieved in the cerebro-spinal fluid, but passage of the drug across the blood- brain barrier increases in meningitis. In the presence of normal hepatic function, erythromycin is concentrated in the liver, bile and spleen.

Protein binding:

70 to 75% protein bound; 85% to α_1 acid glycoprotein and the remainder to albumin.

Metabolism:

>90%, partially inactivated by N-demethylation in the liver but concentration of active drug in bile is high and there is evidence of enterohepatic circulation.

Half-life:

Normal renal function – 1.4 to 2.5 hours

Anuric patients – Approximately 5 hours

Time to peak concentration:

Single dose of 250mg: Approximately 0.8 mcg/mL at 3 hours.

Excretion:

Excreted in the bile; 2 – 5% of an oral dose is excreted in active form in the urine. Erythromycin crosses the placental barrier and is excreted in breast milk.

INDICATIONS:

Erythromycin has been used in the treatment of a wide variety of infections caused by susceptible organisms. Its uses have included the following:

1. Upper Respiratory Tract Infections:

Tonsillitis, peritonsillar abscess, pharyngitis, laryngitis, sinusitis, secondary infections in colds and influenza.

2. Lower Respiratory Tract Infections:

Tracheitis, acute and chronic bronchitis, *Mycoplasma pneumoniae* (lobar pneumonia, bronchopneumonia, primary atypical pneumonia), bronchiectasis, Legionnaires' disease, *Streptococcus pneumoniae,* pneumonia caused by *Chlamydia trachomatis, Nocardia, Actinomyces israelii* and *Coxiella burneti.*

3. Ear and Oral Infections:

Otitis media and otitis externa, mastoiditis, gingivitis, dental abscesses, Vincent's angina.

4. Eye Infections:

Blepharitis, trachoma, neonatal conjunctivitis.

5. Veneral Infections:
Nonspecific urethritis, gonorrhea, syphilis (if the patient is allergic to penicillin), chlamydial infections of the genital tract and lymphogranuloma venereum.
6. Skin and Soft Tissue Infections:
Boils and carbuncles, paronychia, abscesses, pustular acne, impetigo, streptococcal cellulitis, phlegmon, furunculosis, erysipelas, erythrasma., minor infections involving penicillinase – producing *Staphylococcus aureus.*
7. Gastrointestinal Infections:
Cholecystitis, staphylococcal enterocolitis, gastroenteritis caused by *Campylobacter jejuni.*
8. Prophylaxis:
Preoperative and postoperative, trauma, burns, rheumatic fever, bacterial endocarditis.
9. Other Infections:
Osteomyelitis, diphtheria, scarlet fever, whooping cough (pertussis).

CONTRAINDICATIONS:
Patients with known hypersensitivity to erythromycin.
It should also be avoided in patients with existing liver dysfunction or who are currently receiving potentially hepatotoxic drugs.
Concurrent use of astemizole or terfenadine with erythromycin is contraindicated: Concurrent use may increase the risk of cardiotoxicity, such as *torsades de pointes* and ventricular tachycardia, and death.

SIDE EFFECTS / ADVERSE REACTIONS:
Erythromycin and its salts and esters are generally well-tolerated and serious adverse effects are rare. The most frequent side effects of erythromycin preparations are gastrointestinal, e.g. abdominal / stomach discomfort and cramp, nausea, vomiting and diarrhoea. Supra-infection with resistant organisms may occur and there has been a report of pseudomembranous colitis associated with erythromycin use.
Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred. There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.
There have been isolated reports of transient central nervous system side effects including confusion, hallucinations, seizures and vertigo; however, a cause and effect relationship has not been established. Occasional case reports of cardiac arrhythmias, e.g. ventricular tachycardia have been documented in patients receiving erythromycin therapy. There have been isolated reports of other cardiovascular symptoms, e.g. chest pain, dizziness and palpitations; however, a cause and effect relationship has not been established.

Incidence less frequent
Hepatotoxicity
Symptoms include malaise, nausea, vomiting, abdominal cramps, skin rash, and fever. Jaundice may or may not be present. Liver function tests often indicate cholestasis.

Symptoms typically appear within a few days to 1 or 2 weeks after the start of continuous therapy, and are reversible when erythromycin is discontinued.

Incidence rare

Cardiac toxicity, especially QT prolongation and *torsades de pointes* (irregular or slow heart rate; recurrent fainting; sudden death); pancreatitis (severe abdominal pain, nausea and vomiting)

PRECAUTIONS / WARNINGS:

Risk-benefit should be considered when the following medical problems exist:

Cardiac arrhythmias, history of, or QT prolongation: **Patients with a history of cardiac arrhythmias or QT prolongation may be at risk for arrhythmias or *torsades de pointes* while receiving high doses of erythromycin.**

Loss of hearing: **Patients with a history of hearing loss may be at increased risk of further hearing loss, especially if the patient has renal or hepatic function impairment, is elderly, and is receiving high doses of erythromycin.**

Liver impairment / hepatotoxic agents: **Since erythromycin is excreted principally in the bile, caution should be exercised when administering it to patients with impaired liver function or receiving hepatotoxic agents.**

Superinfection: **The rare possibility of superinfection, caused by overgrowth of non-susceptible bacteria or fungi should be borne in mind during prolonged or repeated therapy, especially when other antibacterial agents are being employed simultaneously.**

Porphyria: **Erythromycin was considered to be unsafe in patients with acute porphyria because it has been associated with acute attacks.**

Use in Pregnancy: **There is no evidence that the use of erythromycin is hazardous in human pregnancy though it does not cross the placental barrier. Animal studies have also revealed no hazard.**

Lactation: **Erythromycin reaches concentrations in human milk higher than those in maternal plasma. However, problems in humans have not been documented.**

Children: **Apart from reduced dosage no special precautions are required.**

The elderly: **No special precautions are required in elderly patients with normal liver function.**

DRUG INTERACTIONS:

Theophylline: Recent studies have shown that the use of erythromycin in patients receiving high doses of theophylline may be associated with an increase in serum theophylline levels and with potential theophylline toxicity. In such cases, the dose of theophylline should be reduced.

Alfentanil: Erythromycins, which are hepatic enzyme inhibitors, may decrease the plasma clearance and prolong the duration of action of alfentanil.

Carbamazepine or Valproic acid: Erythromycins may inhibit carbamazepine and valproic acid metabolism, resulting in increased anticonvulsant plasma concentrations and toxicity.

Chloramphenicol or Lincomycins: Erythromycins may antagonize the effects of chloramphenicol or lincomycins.
Cyclosporine: Erythromycin has been reported to increase cyclosporine plasma concentrations and may increase the risk of nephrotoxicity.
Digoxin: Concurrent use of oral antibiotics may increase serum digoxin concentrations.
Ergotamine: Erythromycin inhibits the metabolism of ergotamine and has been reported to increase the vasospasm associated with ergotamines.
Lovastatin: Concurrent use of lovastatin with erythromycin may increase the risk of rhabdomyolysis.
Midazolam or Triazolam: Concurrent use with erythromycin may decrease the clearance of these medications, increasing the pharmacological effect of midazolam or triazolam.
Ototoxic medications, other: Concurrent use of other ototoxic medications with high-dose erythromycin in patients with renal function impairment may increase the potential for ototoxicity.
Warfarin:
Use of erythromycin in patients receiving chronic warfarin therapy may result in increased risk of hemorrhage.

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION:
Adults: Mild to moderate infection, 250 mg every 6 hours or 500 mg every 12 hours. In very severe infections, the dosage may be increased to 4 g or more daily in divided doses.
Children: 30 mg / kg / day in divided doses. In very severe infection this may be increased to 50 mg / kg or even 100 mg/kg/day given in 2 or 3 divided doses.
The period of treatment is 6-10 days for upper and lower respiratory tract infections. In cases of infection due to β-haemolytic Streptococci of group A, the treatment should be extended to 10 days, and in cases of *Mycoplasma pneumoniae* to 10-14 days. Optimum serum levels of erythromycin are attained when Elthrocin is taken in the fasting state or immediately before meals.
Skin Infections: Acne: 1 g / day for 1-2 weeks and 0.5 g / day for minimum of 12 weeks. Impetigo: 1 g / day for 10 days. Erysipelas, Phelgmon, Furunculosis, Carbuncles: 2 g / day for 10 days. Erythrasma: 1.5 g / day for 6 days.
Otitis Externa: 1.5 g / day for 6-10 days.
Veneral Infections: Nonspecific urethritis: 1.5 to 2 g / day for 14-21 days. Syphilis: In patients allergic to penicillin, up to 3 g / day in divided doses for 10-20 days.
Lymphogranuloma Venereum: 1.5 g / day for 8-10 days.
Other Infections: Gingivitis: 1 g / day for 6-10 days.
Diphtheria, scarlet fever: 1-1.5 g / day for 10 days.
Trauchoma: 1.5 g / day for 21 days.

Prophylaxis: Preoprerative: 1 g one hour before the procedure followed by 500 mg six hours later.

SYMPTOMS AND TREATMENT FOR OVERDOSE AND ANTIDOTES:

Symptoms:

Acute overdosage may result in reversible hearing loss, severe nausea, vomiting and diarrhoea.

Treatment:

Recommended treatment consists of the following:

To decrease absorption – Evacuating the stomach to eliminate unabsorbed drug.

Specific treatment – Administering epinephrine, corticosteroids, and anti-histamines for allergic reactions.

Supportive care – Using supportive measures as needed. Patients in whom intentional overdose is known or suspected should be referred for psychiatric consultation.

PACKING / PACK SIZES:

250 mg: Blister pack of 10x10's/box, 100x10's/box; Plastic containers of 500's (for export only) and 1000's (for export only).

500 mg: Blister pack of 10's, 10x10's/box, 100x10's/box.

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS:

250 mg: Store in a dry place, below 30°C, in a tight container. Protect from light.

500 mg: Store in a dry place, below 30°C, in a tight container. Protect from light.

SHELF LIFE: 3 years

NAME AND ADDRESS OF MANUFACTURER:

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