1. NAME OF THE MEDICINAL PRODUCT

Erythromax (Erythromycin Stearate Tablets BP 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:

Erythromycin Stearate BP

Eq. to Erythromycin……..500 mg

Excipients……q.s.

Color: Ponceau 4R

List of Excipients:

Excipients	Quantity /Tablet (mg)	Uses
Maize Starch	41.000	Diluent
Docusate Sodium 98%	6.000	Solubility Enhancer
Maize Starch	9.000	Diluent
Purified Water	Q.S.	Binding Solvent
Croscarmellose Sodium (Vivasol)	23.000	Disintegrant
Sodium Starch Glycolate	19.000	Disintegrant
Colloidal Silicon Dioxide (Colloidal Anhydrous Silica) (Light)	9.000	Adsorbent
Talcum (Purified Talc)	19.000	Glidant
Hypromellose (H.P.M.C E 15)	15.7500	Film Forming Polymer
Ponceau 4R Lake	2.000	Colourant
Talcum (Purified Talc)	1.000	Glidant
PEG 6000 (Macrogol)	1.000	Plasticizer
Titanium Dioxide	0.2500	Opacifier
Isopropyl Alcohol*	230.000	Coating Solvent
Dichloromethane (Methylene Chloride) DCM*	400.000	Coating Solvent

3. PHARMACEUTICAL FORM

A Brick red colored caplet shaped film coated tablet, having break line on one side of the 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, 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.

8. Prophylaxis: pre- and post- operative trauma, burns, rheumatic fever.

9. Other infections: osteomyelitis, urethritis, gonorrhoea, syphilis, lymphogranuloma venereum, diphtheria, prostatitis, scarlet fever.

4.2 Posology and method of administration

Posology

For oral administrations.

Adults and children over 8 years: For mild to moderate infections 2g daily in divided doses. Up to 4g daily in severe infections.

Elderly: No special dosage recommendations.

Note: For younger children, infants and babies, Erythroped, erythromycin ethylsuccinate suspensions, are normally recommended. The recommended dose for children age 2-8 years, for mild to moderate infections, is 1 gram daily in divided doses. The recommended dose for infants and babies, for mild to moderate infections, is 500 mg daily in divided doses. For severe infections doses may be doubled.

4.3 Contraindications

Known hypersensitivity to erythromycin.

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

Erythromycin is contraindicated with ergotamine and dihydroergotamine

4.4 Special warning 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. 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.

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.

4.5 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 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.

4.6 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.

4.7 Effects on ability to drive and use machine

None known.

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 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.

4.9 Overdose and treatment

Symptoms: hearing loss, severe nausea, vomiting and diarrhoea.

Treatment: gastric lavage, general supportive measures.

5- Pharmacological Properties:

5.1 Pharmacodynamic Properties:

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

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

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Ingredients	Specification
Maize Starch	BP
Docusate Sodium 98%	BP
Purified Water	BP
Croscarmellose Sodium (Vivasol)	BP
Sodium Starch Glycolate	BP
Colloidal Silicon Dioxide (Colloidal Anhydrous Silica) (Light)	BP
Talcum (Purified Talc)	BP
Hypromellose (H.P.M.C E 15)	BP
Ponceau 4R Lake	IHS
PEG 6000 (Macrogol)	BP
Titanium Dioxide	BP
Isopropyl Alcohol*	BP
Dichloromethane (Methylene Chloride) DCM*	BP

5.2 Incompatibilities

Not applicable.

5.3 Shelf life

36 months from the date of manufacture

5.4 Special precautions for storage

Store below 30°C, Protect from light & moisture.

5.5 Nature and contents of container <and special equipment for use, administration or implantation>

10 Tablets packed in one Alu-Alu Blister. Such 10 Alu-Alu Blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

Primary Packaging: Alu-Alu blisters contain 10 a Brick red coloured caplet shaped film coated tablet having break line on one side of the tablets.

Secondary Packaging: 10 x 10 Alu-Alu Blisters packed in unit printed duplex board carton along with its package insert.

The container closure system consists of the following:

1) **Primary packaging:**

   Printed Aluminium Foil

   Plain Aluminium Base

2) **Secondary packaging**

   Shipper of Alu-Alu blister Pack

   Pack Insert

   Multipack style: 3 X 10 / ALU-ALU

   3 X 10/ALU-PVC

Note: All pack style may not be marketed

5.6 Special precautions for disposal

No special requirements.

6. MANUFACTURER

Globela Pharma Pvt. Ltd.

Plot No. 357-358, GIDC,

Sachin, Surat,Gujarat, India

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