

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of Medicinal Product

SOFTHEALTH ERYTHROMYCIN 500

ERYTHROMYCIN STEARATE TABLETS BP 500MG

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Composition of the Drug product:

Each film coated tablets contains:

Erythromycin (as Stearate) BP

Equivalent to Erythromycin 500 mg

Excipients Q.S.

Colour: Titanium Dioxide BP

Qualitative & Quantitative Composition Formula:

Batch Size: 1,00,000 Tablets

Sr. No.	Name of raw material	Specification	Label Qty/Tab (mg)	% Overages	Qty per tablet with Overages (mg)	Std. Qty for 1.0 Lac (kg)	Function
1.	*Erythromycin Stearate Eq. to Erythromycin	BP	693.46 MG	8.16 %	750.04	75.004	Active
2.	Lactose	IHS			117.96	11.796	Diluent
3.	Croscarmellose Sodium	BP			60.00	6.00	Disintegrant
4.	Colloidal silicon dioxide	BP			6.00	0.60	Absorbent
5.	Talcum	BP			6.00	0.60	Glidant
6.	Kyron T-314	USP-NF			10.00	1.00	Disintegrant
Total weight of Uncoated tablet					950.0 mg	95.00 kg	
7.	Isopropyl alcohol	BP		---	18.20 ml	18.20 ml	Solvent

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8.	Ready Mix of white (Film Coating)	IH		---	24.00	24.00	Colouring agent
9.	Methylene Chloride	BP		---	27.40 ml	27.40 ml	Solvent
Total weight of Tablets					974.00 mg	97.40 kg	

Note: * Compensate the qty of Actives with lactose to maintain the average weight.

3. Pharmaceutical form

Film coated Tablets

A White coloured, Caplet shaped, Biconvex, film coated tablet having Break-line on one side.

4. Clinical Particulars

4.1 Therapeutic indications

For the prophylaxis and treatment of infections caused by erythromycin-sensitive organisms (see section 5.1).

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

Consideration should be given to official guidance on the appropriate use of antimicrobial agents.

4.2 Posology and method of administration

Posology

Adults and children over 8 years: For mild to moderate infections 1-2g daily in divided doses. Up to 4g daily in severe infections.

Elderly: No special dosage recommendations.

Paediatric population

Note: For younger children, infants and babies, erythromycin suspensions is 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.

Method of administration

For oral administrations.

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 should not be given to patients with a history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see section 4.4 and 4.5).

Erythromycin should not be given to patients with electrolyte disturbances (hypokalaemia, hypomagnesaemia due to the risk of prolongation of QT interval).

Erythromycin is contraindicated with ergotamine and dihydroergotamine.

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.

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.

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.

Cardiovascular Events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in patients treated with macrolides including erythromycin (see sections 4.3, 4.5 and 4.8). Fatalities have been reported

Erythromycin should be used with caution in the following:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.
- Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.3 and 4.5).
- Elderly patients may be more susceptible to drug- associated effects on the QT interval (see section 4.8).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including erythromycin. Consideration of these findings should be balanced with treatment benefits when prescribing erythromycin.

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).

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.

Paediatric population

There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. Epidemiological studies including data from meta-analyses suggest a 2-3-fold increase in the risk of IHPS following exposure to erythromycin in infancy. This risk is highest following exposure to erythromycin during the first 14 days of life. Available data suggests a risk of 2.6% (95% CI: 1.5 -4.2%) following exposure to erythromycin during this time period. The risk of IHPS in the general population is 0.1-0.2%. . 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 pimozone 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.

Oral anticoagulants: there have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants (e.g. warfarin, rivaroxaban) 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 (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

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.

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.

Erythromycin has been reported to cross the placental barrier in humans, but foetal plasma levels are generally low.

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.

Breast-feeding

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.

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).

Fertility

No data available

4.7 Effects on ability to drive and use machines

Erythrocin has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The list of undesirable effects shown below is presented by system organ class, MedDRA preferred term, and frequency using the following frequency conventions:

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Rare	*Pseudomembranous colitis
Blood and lymphatic system disorders	Not known	Eosinophilia.
Immune system disorders	Not known	Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.
Psychiatric disorders	Not known	Hallucinations
Nervous system disorders	Not known	**Seizures, confusion and vertigo
Eye disorders	Not known	Mitochondrial Optic Neuropathy
Ear and labyrinth disorders	Not known	Deafness, tinnitus ***Reversible hearing loss
Cardiac disorders	Not known	QTc interval prolongation, torsades de pointes, palpitations, and cardiac rhythm disorders including ventricular tachyarrhythmias. Cardiac arrest, ventricular fibrillation.
Vascular disorders	Not known	Hypotension.
Gastrointestinal disorders	Not known	Infantile hypertrophic pyloric stenosis. ****Pancreatitis, diarrhoea, anorexia, upper abdominal discomfort, nausea, vomiting
Hepatobiliary disorders	Not known	Hepatic failure, hepatocellular hepatitis (see section 4.4), hepatomegaly, hepatic dysfunction,

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		cholestatic hepatitis, jaundice.
Skin and subcutaneous tissue disorders	Not known	Acute generalised exanthematous pustulosis (AGEP). Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioedema, skin eruptions, pruritus, urticaria, exanthema.
Renal and urinary disorders	Not known	Interstitial nephritis
General disorders and administration site conditions	Not known	Chest pain, fever, malaise.
Investigations	Not known	Increased liver enzyme values.

* Has been rarely reported in association with erythromycin therapy (see section 4.4).

** There have been isolated reports of transient central nervous system side effects, however, a cause and effect relationship has not been established.

*** There have been isolated reports, occurring chiefly in patients with renal insufficiency or high doses.

**** The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

4.9 Overdose

Symptoms

Hearing loss, severe nausea, vomiting and diarrhoea.

Management

Gastric lavage, general supportive measures.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01FA01

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 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.

Susceptibility testing breakpoints:

EUCAST clinical MIC breakpoints for erythromycin (Version 11.0, valid from 2021-01-01):

Pathogen	Susceptible (mg/L)	Resistant (mg/L)
<i>Staphylococcus</i> spp.	≤1	>2
<i>Streptococcus</i> groups A,B,C,G	≤ 0.25	> 0.5
<i>Streptococcus pneumoniae</i>	≤ 0.25	> 0.5
<i>Haemophilus influenzae</i>	Note ¹⁾	Note ¹⁾
<i>Moraxella catarrhalis</i>	≤ 0.25	> 0.5
<i>Campylobacter jejuni</i>	≤ 4	> 4
<i>Campylobacter coli</i>	≤ 8	> 8

<i>Non species related breakpoints</i>	<i>IE*</i>	<i>IE*</i>
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1) Clinical evidence for the efficacy of macrolides in H. influenza respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFS) should be used to detect strains with acquired resistance. The ECOFF for erythromycin is 16 mg/l.

**"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug. A MIC with a comment but without an accompanying S, I or R categorisation may be reported.*

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is known and the utility of the agent in at least some types of infections is questionable.

5.2 Pharmacokinetic properties

Absorption

It is absorbed from the small intestine.

Distribution

It is widely distributed throughout body tissues.

Biotransformation

Little metabolism occurs and only about 5% is excreted in the urine.

Elimination

The elimination half-life is approximately two hours. 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

Sr. No.	Ingredients Name	Specification
1.	Lactose	IHS
2.	Croscarmellose Sodium	BP
3.	Colloidal silicon dioxide	BP
4.	Talcum	BP
5.	Kyron T-314	USP-NF
6.	Isopropyl alcohol	BP
7.	Ready Mix of white (Film Coating)	IH
8.	Methylene Chloride	BP

6.2 Incompatibilities: Not Applicable

6.3 Shelf-life: 36 Months

6.4 Special precautions for storage:

Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of container:

ERYTHROMYCIN STEARATE TABLETS BP 500MG is packed in an Alu-Alu Blister of 10 tablets, such 1 Blister are packed in a primary carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special instructions for use/handling

7- Marketing Authorization Holder:

**SOFTHEALTH PHARMACEUTICALS LIMITED
38, Fatai Irawo Street, Ajao Estate, Lagos, Nigeria.**

**8- Marketing Authorization Number (s):
Product license / registration Number (s)**

**9- Manufacturer Name:
RELAX BIOTECH PVT. LTD.
862/1, G.I.D.C., Makarpura,
Vadodara-390010. Gujarat, India,**

10- Date of first authorization/renewal of the authorization:

11- Date of revision of the text:
