

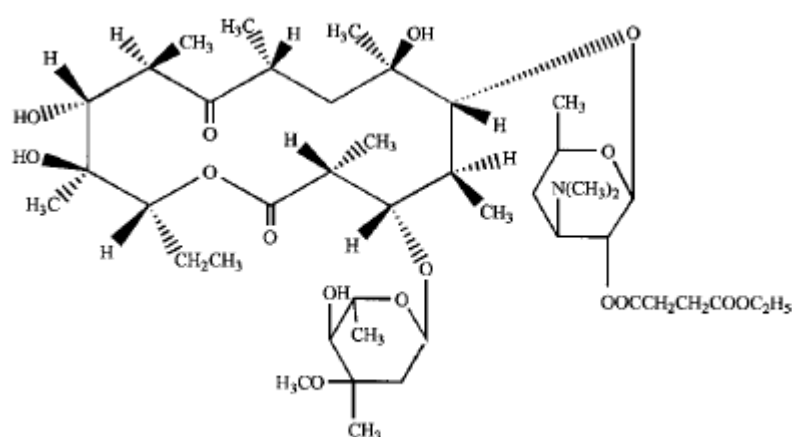
PRODUCT INFORMATION

**EES 400 mg tablets (erythromycin 400 mg as ethyl succinate),
EES 200mg/5mL granules (erythromycin as ethylsuccinate) for oral liquid
EES 400mg/5mL granules (erythromycin as ethylsuccinate) for oral liquid**

NAME OF THE MEDICINE

Erythromycin ethylsuccinate

Erythromycin ethylsuccinate is known chemically as erythromycin 2'-(ethylsuccinate). The molecular formula is $C_{43}H_{75}NO_{16}$ and the molecular weight is 862.06. The structural formula is:



CAS Number: 1264-62-6

DESCRIPTION

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. EES products contain the ethylsuccinate ester of erythromycin. The tablets are intended primarily for adult use. The granules are intended primarily for paediatric use but may also be used by adults.

EES 400 mg tablets are available for oral administration in a strength of 400 mg of erythromycin ethylsuccinate with the following inactive ingredients: Sucrose, sodium citrate, maize starch, polacrillin potassium, magnesium stearate, hypromellose, hydroxypropylcellulose, propylene glycol, macrogol 400, sorbic acid, and macrogol 8000. Colours used are allura red (129), brilliant scarlet (124), indigo carmine (132) and sunset yellow (110), titanium dioxide (171).

EES 200mg/5mL Granules are available for oral administration in a strength of 200mg erythromycin ethylsuccinate per 5mL once reconstituted, with the following inactive ingredients: Carmellose sodium, sodium citrate, aluminium magnesium silicate, Colour - erythrosine CI145430, Flavour - cherry imitation and sweetener – sucrose and saccharin sodium.

EES 400mg/5mL Granules are available for oral administration in a strength of 400mg erythromycin ethylsuccinate per 5mL once reconstituted, with the following inactive ingredients: Carmellose sodium, sodium citrate, citric acid, aluminium magnesium silicate, Colour - carmoisine CI14720, Flavour - cherry imitation and sweeteners sodium cyclamate and saccharin sodium and sucrose.

PHARMACOLOGY

Following oral administration, erythromycin ethylsuccinate is absorbed intact and undergoes hydrolysis to yield the active erythromycin base. Individual peak serum levels show considerable variability; the peak after each dose occurs in 1-2 hours. The extent of plasma protein binding has been variably reported but is probably of the order of 75%. Erythromycin diffuses readily into most body fluids with the exception of cerebrospinal fluid, synovial fluid and vitreous humor. In the presence of normal renal function, the plasma half life is approximately 1.4 hours; this may increase to 6 hours in anuric patients but does not usually require dosage adjustment. Erythromycin is not removed by dialysis.

In the presence of normal hepatic function, erythromycin is concentrated in the liver and high concentrations appear in the bile. However, approximately 1.5% of the absorbed erythromycin can be recovered unchanged in bile over a period of 8 hours. Substantial quantities appear in the faeces and probably represent the unabsorbed drug plus the drug excreted into the bile. Approximately 5% of an orally administered dose appears in the urine. A large proportion of the absorbed drug remains unaccounted for and is presumably metabolised, probably in the liver.

Erythromycin appears in breast milk at levels which are approximately 50% of the plasma concentration. It crosses the placenta and fetal plasma levels are usually 5%-20% of the maternal plasma concentration.

Microbiology

Erythromycin binds to the 50S ribosomal sub-units of susceptible bacteria and suppresses protein synthesis. The mode of action of erythromycin is by inhibition of the protein synthesis without affecting nucleic acid synthesis. Erythromycin is usually active in vitro against the following Gram positive and Gram negative organisms:

Streptococcus pyogenes
Alpha-haemolytic streptococci (viridans group)
Staphylococcus aureus
Streptococcus pneumoniae
Corynebacterium diphtheriae (as an adjunct to antitoxin)

Corynebacterium minutissimum
Listeria monocytogenes
Clostridium tetani
Neisseria gonorrhoeae
Bordetella pertussis
Haemophilus influenzae (some strains are resistant)
Legionella pneumophila
Treponema pallidum
Chlamydia trachomatis
Mycoplasma pneumoniae
Campylobacter jejuni (in severe or prolonged cases)
Ureaplasma Urealyticum

Not all strains of the organisms listed above are sensitive, and culture and susceptibility testing should be done. Several strains of *Haemophilus influenzae* and staphylococci have been found to be resistant to erythromycin. Staphylococci resistant to erythromycin may emerge during a course of therapy. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin and chloramphenicol.

Susceptibility Testing:

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regular updated, recognized and standardised method (eg.CLSI).

Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

- A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.
- A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation.
- A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable: other therapy should be selected.

Note 1: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Note 2: Many strains of *Haemophilus influenzae* are resistant to erythromycin alone but are susceptible to erythromycin and sulfonamides together. Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Culture and susceptibility testing should be performed.

INDICATIONS

Streptococcus pyogenes (Group A beta-haemolytic streptococcus):

Upper and lower respiratory tract, skin and soft tissue infections of mild to moderate severity. When oral medication is preferred for treatment of the above conditions, penicillin G, V, or erythromycin are alternate drugs of choice.

When oral medication is given, the importance of strict adherence by the patient to the prescribed dosage regimen must be stressed. A therapeutic dose should be administered for at least 10 days.

Alpha-haemolytic streptococci (viridans group):

Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been suggested by the American Heart Association and the American Dental Association for use in a regimen for prophylaxis against bacterial endocarditis in patients hypersensitive to penicillin, who have congenital heart disease, or rheumatic or other acquired valvular heart disease when they undergo dental or surgical procedures of the upper respiratory tract. Erythromycin is not suitable prior to genitourinary or gastrointestinal tract surgery.

Staphylococcus aureus:

Acute infections of skin and soft tissue of mild to moderate severity. Not all strains are sensitive, and cultures and sensitivity tests should be done. Resistant organisms may emerge during treatment.

Streptococcus pneumoniae (Diplococcus pneumoniae):

Upper respiratory tract infections (e.g. otitis media, pharyngitis) and lower respiratory tract infections (e.g. pneumonia) of mild to moderate degree.

Mycoplasma pneumoniae (Eaton agent, PPLO):

For respiratory infections due to this organism.

Haemophilus influenzae:

For upper respiratory tract infections of mild to moderate severity. Not all strains of this organism are susceptible at the erythromycin concentrations ordinarily achieved.

Treponema pallidum:

Erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Neisseria gonorrhoeae:

Erythrocin I.V. (erythromycin lactobionate for injection) in conjunction with erythromycin orally, as an alternative drug in treatment of acute uncomplicated gonorrhoea in female patients with a history of hypersensitivity to penicillin.

Before treatment of gonorrhoea, patients who are suspected of also having syphilis should be adequately evaluated including a microscopic examination for *T. pallidum* (by

immunofluorescence or darkfield) before receiving erythromycin and monthly serologic tests should be made for a minimum of 4 months.

Corynebacterium diphtheriae, C. minutissimum, C.(propionibacterium) acnes:

As an adjunct to diphtheria antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers; in the treatment of erythrasma; and as adjunct to therapy of moderate to severe acne.

Listeria monocytogenes:

Infections due to this organism.

Bordetella pertussis:

Erythromycin produces early elimination of the causative organism from the nasopharynx although the clinical course of the disease is not altered; therapeutic doses should be continued for at least 10 days.

Clostridium tetani:

In vitro, *Clostridium tetani* is sensitive to erythromycin. In persons with hypersensitivity to penicillin, erythromycin may be used in the usually recommended doses for 5 days for prophylaxis. However, as the value of antibiotic prophylaxis in tetanus is not unequivocally established, wounds should be regularly examined.

Legionnaires' Disease:

Although no controlled clinical efficacy studies have been conducted, in vitro and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

Non-gonococcal Urethritis:

Chlamydia trachomatis and *Ureaplasma urealyticum* have been shown to be sensitive to erythromycin and clinical studies have demonstrated its efficacy in urethritis due to these organisms. A minimum of ten days therapy appears to be required.

Chlamydia trachomatis infection (excluding Non-gonococcal Urethritis):

Erythromycin has been shown to be effective in the treatment of trachoma or inclusion-body conjunctivitis, acute inclusion conjunctivitis of the newborn (inclusion blennorrhoea) and pneumonia in infants caused by *Chlamydia trachomatis*.

Campylobacter fetus (subspecies) jejuni:

Infections due to this organism when antibiotic therapy is indicated.

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to erythromycin or any of excipients in the formulation, or to other antibiotics from the macrolide family.

Severely impaired hepatic function.

Concurrent treatment with cisapride, pimozone, and ergotamine or dihydroergotamine is contraindicated. (See **PRECAUTIONS**)

PRECAUTIONS

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice occurring in patients receiving oral erythromycin products. Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored for creatine kinase (CK) and serum transaminase levels. (See **Interactions with other medicines**)

The use of erythromycin can lead to the development of severe colitis as a result of colonisation with *C. difficile*, a toxin-producing organism. The colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can be fatal. If significant diarrhoea occurs (this may, however, begin up to several weeks after cessation of antibiotic therapy) erythromycin should be discontinued. This may be sufficient treatment in the early stages although cholestyramine orally may help by binding the toxin in the colonic lumen. In moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered.

Erythromycin appears to be principally degraded and excreted by the liver. Therefore it should be avoided in patients with impaired hepatic function.

Overgrowth of non-susceptible bacteria or fungi may occur during prolonged or repeated therapy. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

Oral erythromycin is not considered to be the antibiotic of choice in critically ill patients.

When indicated, incision or drainage or other surgical procedures should be performed in conjunction with antibiotic therapy.

There have been reports that erythromycin may aggravate the weakness of patients with myasthenia gravis.

Effects on the Neonate

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.

Effects on Fertility

There was no apparent effect on male or female fertility in rats treated with erythromycin base by oral gavage at 700 mg/kg/day (approximately 9 times the human dose).

Use in Pregnancy: Category A

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

No evidence of teratogenicity or embryotoxicity was observed when erythromycin base was given by oral gavage to pregnant rats and mice at 700 mg/kg/day (approximately 9 times the maximum human dose), and to pregnant rabbits at 125 mg/kg/day (approximately 1.5 times the maximum human dose).

A slight reduction in birth weights was noted when female rats were treated prior to mating, during mating, gestation and lactation at an oral dosage of 700 mg/kg/day of erythromycin base; weights of the offspring were comparable to those of the controls by weaning. No evidence of teratogenicity or effects on reproduction was noted at this dosage. When administered during late gestation and lactation periods, this dosage of 700 mg/kg/day (approximately 9 times the maximum human dose) did not result in any adverse effects on birth weight, growth and survival of offspring.

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 fetal plasma levels are generally low.

Erythromycin should be used by women during pregnancy only if clearly needed.

Use in Lactation

Erythromycin is excreted in breast milk. Caution should be exercised when erythromycin is administered to a nursing woman.

Carcinogenicity

Long-term (2 year) oral studies conducted in rats up to about 400 mg/kg/day and in mice up to about 500 mg/kg/day with erythromycin stearate did not provide evidence of tumourigenicity.

Genotoxicity

Erythromycin was not genotoxic in assays for bacterial and mammalian mutagenicity and for clastogenicity *in vitro*. The clastogenic potential of erythromycin has not been investigated *in vivo*.

Interactions with other Medicines

There have been reports that there is a rise in serum levels of cyclosporin, phenytoin, hexobarbital, carbamazepine, alfentanil, disopyramide, bromocriptine, valproate, methylprednisolone, vinblastine, sildenafil, cilostazol, quinidine, tacrolimus rifabutin, verapamil and diltiazem (drugs metabolised by the cytochrome P450 system) during concomitant administration of erythromycin.

Theophylline:

Recent data from studies of erythromycin reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase of 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 that when oral erythromycin is given concurrently with theophylline there is a significant decrease in erythromycin serum concentrations. This decrease could result in subtherapeutic concentrations of erythromycin.

Carbamazepine:

Erythromycin administration in patients receiving carbamazepine has been reported to cause increased serum levels of carbamazepine with subsequent development of signs of carbamazepine toxicity.

Digoxin:

Concomitant administration of erythromycin and digoxin has been reported to result in elevated serum digoxin levels.

Anticoagulants:

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly.

Triazolam:

Triazolam plasma concentrations may approximately double when erythromycin is co-administered, due to a reduction in clearance and increase in elimination half-life but drug accumulation has not been observed with repeated dosing. Therefore consideration of dose reduction may be appropriate in patients treated concurrently with triazolam and erythromycin.

Ergotamine / dihydroergotamine:

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterised by severe peripheral vasospasm and dysaesthesia (see **CONTRAINDICATIONS**).

Zopiclone:

Erythromycin has been reported to decrease the clearance of zopiclone and thus may increase the pharmacodynamic effects of this drug.

Cisapride:

Elevated cisapride levels have been reported in patients receiving erythromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsade de pointes. Similar effects have been observed in patients taking pimozide and clarithromycin, another macrolide antibiotic.

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.

Colchicine:

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine.

Interactions with laboratory tests

Erythromycin interferes with the fluorimetric determination of urinary catecholamines.

ADVERSE EFFECTS

The most frequent side effects of erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose-related. Nausea, vomiting and diarrhoea occur infrequently with usual oral doses.

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving oral erythromycin products. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur.

During prolonged or repeated therapy, there is a possibility of overgrowth of non-susceptible bacteria or fungi. If such infections occur, the drug should be discontinued and appropriate therapy instituted.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred. Skin reactions ranging from mild eruptions to erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely.

Occasional case reports of cardiac arrhythmias, such as ventricular tachycardia have been documented in patients receiving erythromycin therapy. There have been isolated reports of

other cardiovascular symptoms such as chest pain, dizziness and palpitations; however a causal relationship has not been established.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

Central nervous system side effects, including seizures, hallucinations, confusion, vertigo and tinnitus have been reported in occasional patients; however, a cause and effect relationship has not been established.

There have been rare reports of pancreatitis and convulsions.

Infantile hypertrophic pyloric stenosis (IHPS):

7 out of 157 [5%] newborns developed severe non-bilious vomiting or irritability with feeding and IHPS who were given oral erythromycin for pertussis prophylaxis. The relative risk of IHPS was increased 6.8 fold (95% CI=3-16) compared to a retrospective cohort of infants.

There have been reports of interstitial nephritis coincident with erythromycin use.

DOSAGE AND ADMINISTRATION

Some clinicians believe that twice daily dosing is inadequate for all but minor infections caused by highly susceptible organisms. Twice daily dosing should not be employed when more than 1.6 g of erythromycin as the ethylsuccinate per day is required.

EES tablets and granules may be administered without regard to meals.

Adults

400 mg erythromycin as the ethylsuccinate every 6 hours is the usual dose. Dosage may be increased up to 4.0 g per day according to the severity of the infection. If a twice daily dosage is desired one-half of the total daily dose, provided it does not exceed 1.6 g, may be given every 12 hours.

Children

Age, weight and severity of the infection are important factors in determining the proper dosage. In mild to moderate infections the usual dosage is 30 to 50 mg/kg/day in divided doses. For more severe infections this dosage may be doubled.

The maximum calculated dose for children should not exceed the maximum dose as specified above for adults.

The following dosage schedule is suggested for mild to moderate infections:

<u>Body Weight (kg)</u>	<u>Total Daily Dose</u>
Under 4.5	30-50 mg/kg
4.5 to 6.8	200 mg
6.8 to 11	400 mg
11 to 23	800 mg
23 to 45	1200 mg
Over 45	1600 mg

In the treatment of streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least 10 days. In continuous prophylaxis against recurrence of streptococcal infections in persons with a history of rheumatic heart disease, the usual dosage is 400 mg twice a day.

When used prior to a dental or upper respiratory tract surgical procedure to prevent endocarditis in patients at risk (see under **INDICATIONS** Alpha- haemolytic streptococci), a recommended schedule for adults is 1.6 g (20 mg/kg for children) 1.5 - 2 hours before the procedure and 800 mg every 6 hours for 6 doses after the procedure.

Erythromycin should be used in mycoplasmal and chlamydial infections at a dosage of 800 mg six hourly for a period of 7 days, or alternatively 400 mg six hourly daily for 14 days.

For the treatment of primary syphilis, adults should be given 48-64 g in divided doses over a period of 15 days.

For severe acne, 400 mg 4 times/day for 2 weeks and then adjust the dose every 4-6 weeks, depending on clinical response. Therapy should be continued for at least three months.

For Legionnaires' Disease: Although optimal doses have not been established, doses utilised in reported clinical data indicate a dosage of 0.8- 1.6 grams six hourly for 14 days.

OVERDOSAGE

Reports indicate that the ingestion of large amounts of erythromycin can be expected to produce gastrointestinal distress, hearing problems and other adverse effects (see **ADVERSE EFFECTS**). Allergic reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures. Erythromycin serum levels are not appreciably altered by haemodialysis or peritoneal dialysis.

For advice on the management of overdose please contact the Poisons Information Centre. In Australia please call 13 11 26 and in New Zealand 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

EES 400 mg tablets

Film coated tablets, each containing 400mg of erythromycin as erythromycin ethylsuccinate in bottles of 25.

EES 200mg/5mL Granules

Granules for reconstitution with water to make 100mL of 200 mg (erythromycin) per 5 mL cherry flavoured suspension.

EES 400mg/5mL Granules

Granules for reconstitution with water to make 100mL of 400 mg (erythromycin) per 5 mL cherry flavoured suspension.

Instructions for reconstituting granules

Add 77 mL of water in small volumes and shake vigorously. When reconstituted, the suspension should be refrigerated (but not frozen) and used within ten days.

All presentations: Store below 30°C.

After reconstitution of the granules, store at 2-8°C (not frozen) for a maximum of 10 days.

NAME AND ADDRESS OF THE SPONSOR

Link Medical Products Pty Ltd.
18/6A Prosperity Parade
Warriewood NSW 2102

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE - S4

DATE OF APPROVAL

Date of TGA Approval

08 January 2008

Date of most recent amendment

13 Sep 2010

Version 02