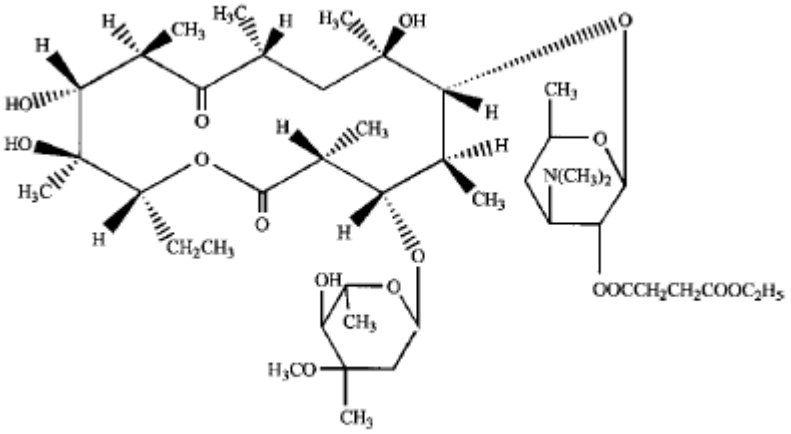
PRODUCT INFORMATION

EES® (erythromycin as ethyl succinate) granules for oral liquid

NAME OF THE MEDICINE

Erythromycin ethyl succinate

Erythromycin ethyl succinate is known chemically as erythromycin 2'-(ethyl succinate). 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 ethyl succinate ester of erythromycin.

EES 200 mg/5 mL granules are available for oral administration in a strength of 200 mg erythromycin (as ethyl succinate) per 5 mL once reconstituted, with the following inactive ingredients: carmellose sodium, sodium citrate dihydrate, aluminium magnesium silicate, erythrosine CI145430 (colouring agent), cherry imitation (flavouring agent), sucrose and saccharin sodium (sweeteners).

EES 400 mg/5 mL granules are available for oral administration in a strength of 400 mg erythromycin (as ethyl succinate) per 5 mL once reconstituted, with the following inactive ingredients: carmellose sodium, sodium citrate dihydrate, citric acid, aluminium magnesium silicate, carmoisine CI14720 (colouring agent), cherry imitation (flavouring agent) and sodium cyclamate, saccharin sodium and sucrose (sweeteners).

PHARMACOLOGY

Pharmacokinetics

Absorption

Following oral administration, erythromycin ethyl succinate 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.

Distribution

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.

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 (see **PRECAUTIONS**).

Elimination

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.

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.

Susceptibility testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regular updated, recognised and standardised method (e.g. 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 IV (erythromycin lactobionate for injection) in conjunction with erythromycin orally, as an alternative in the 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 10 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 the case of:

- Hypersensitivity to erythromycin or any of excipients in the formulation (see **DESCRIPTION**)
- Hypersensitivity to other antibiotics from the macrolide family
- Severely impaired hepatic function
- Congenital or acquired QT interval prolongation
- Concurrent treatment with ergotamine or dihydroergotamine (see **INTERACTIONS WITH OTHER MEDICINES**)
- Disturbances of the electrolyte balance (especially in the case of hypokalaemia and hypomagnesaemia)
- Clinically relevant cardiac arrhythmias (e.g. ventricular arrhythmias) or in severe congestive heart failure (NYHA IV)
- Concomitant intake of medicinal products, which can lead to prolongation of the QT interval and under some circumstances to life-threatening ventricular arrhythmia (torsade de pointes) e.g. terfenadine, astemizole, domperidone, cisapride, pimozide, class IA and III antiarrhythmics (e.g. disopyramide), certain neuroleptics, tri- and tetracyclic antidepressants, arsenic trioxide, methadone, budipine, certain

fluoroquinolones, imidazole anti-mycotics and anti-malarials (e.g. pentamidin i.v.) (see **INTERACTIONS WITH OTHER MEDICINES**)

- Concomitant use of simvastatin, lovastatin or atorvastatin. Treatment with these agents should be interrupted while taking erythromycin (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

QT prolongation

Prolongation of the QT interval and development of ventricular arrhythmias (some of which have been fatal), including atypical ventricular tachycardia (torsades de pointes), have been reported with the administration of erythromycin. Therefore, use of erythromycin is contraindicated in patients with high risk factors for cardiac arrhythmia (see **CONTRAINDICATIONS**). Elderly patients may be more susceptible to drug-associated effects on the QT interval.

If during therapy with erythromycin symptoms such as palpitations, dizziness or syncope occur which can be signs of arrhythmia, an investigation of the patient including Electrocardiogram and determination of the QT interval should be initiated immediately.

Electrolyte disturbances promote the probability of cardiac arrhythmia. In the case of risk factors for electrolyte disturbances (such as diuretic/laxative medication, vomiting, diarrhoea, use of insulin in emergency situations, renal diseases or anorectic conditions), adequate laboratory tests and if necessary an adequate electrolyte balance should be carried out.

Patients with impaired hepatic function/liver damage

There have been reports of hepatic dysfunction, including increased liver enzymes, hepatomegaly and hepatocellular and/or cholestatic hepatitis with or without jaundice, in patients receiving oral erythromycin products (see **ADVERSE EFFECTS**). Patients should be informed to terminate the therapy and seek medical advice if signs and symptoms of liver disease such as loss of appetite, jaundice, dark colouring of the urine and itching or pressure sensitivity of the stomach develop.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. Erythromycin is contraindicated in severe hepatic impairment (see **CONTRAINDICATIONS**).

Patients with existing liver damage and allergies may be at higher risk of intrahepatic cholestasis and cholestatic jaundice due to sensitisation, resulting in colicky abdominal pain, nausea, vomiting, urticaria, eosinophilia and fever. Although these reactions can occur after initial administration, the risk increases with repeated administration and therapy lasting longer than 10 days (see **ADVERSE EFFECTS**).

Musculature and nervous system

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with simvastatin, lovastatin or atorvastatin (see **INTERACTIONS WITH OTHER MEDICINES**). The concomitant use of these medicines with erythromycin is contraindicated (see **CONTRAINDICATIONS**).

Patients taking other statins and erythromycin concomitantly should be instructed by the physician to pay attention to signs of myopathy (e.g. inexplicable muscle pain or weakness or dark coloured urine). If myopathy occurs, the intake of the statin has to be stopped immediately.

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

Clostridium difficile-associated diseases
The use of erythromycin can lead to the development of severe colitis as a result of colonisation with *C. difficile*, a toxin-producing organism. Colitis, which may or may not be accompanied by the formation of a pseudomembrane in the colon, can range in severity from mild diarrhoea to fatal colitis. If significant diarrhoea occurs, erythromycin should be discontinued (diarrhoea however, may begin several weeks to over two months after cessation of antibiotic therapy). 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.

Medicines which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Allergic reactions
With the administration of erythromycin, severe, life-threatening allergic reactions may occur, e.g. severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis (especially in children of all ages), as well as angioneurotic oedema or anaphylaxis. A cross allergy in patients with hypersensitivity to macrolide antibiotics can exist, so in patients with known hypersensitivity to macrolides or related substances (e.g. ketolides), special caution is recommended. At first signs of hypersensitivity, erythromycin has to be stopped immediately and necessary symptomatic emergency measures initiated.

Prolonged or repeated therapy
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.

In the case of a treatment duration longer than 3 weeks, it is recommended that whole blood count and hepatic and renal function tests be performed at regular intervals.

Eye disorder
There is a risk for developing visual impairments after exposure to erythromycin. For some patients, a pre-existing dysfunction in mitochondrial metabolism from genetic causes such as Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) might play a contributing role.

Pneumonia
Due to very common resistance of *Streptococcus pneumoniae* against macrolides, erythromycin is not the first choice therapy in case of ambulant acquired pneumonia. In hospital acquired pneumonia, erythromycin should only be used in combination with other antibiotics.

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.

Vomiting and diarrhoea
Use of erythromycin can cause vomiting and diarrhoea (see **ADVERSE EFFECTS**), impairing the efficacy of this and other concomitantly taken medicines.

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 does not reach the fetus in adequate concentration to prevent congenital syphilis. Newborns of mothers treated with oral erythromycin against early syphilis during pregnancy, will require treatment with an appropriate antibiotics, e.g. penicillin.

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

Use in lactation

Erythromycin is concentrated in breast milk and adverse effects have been seen in breast-fed infants including gastrointestinal disturbances, pyloric stenosis (see **Paediatric use**), sensitisation or colonisation with fungi. Caution should be exercised when erythromycin is administered to a nursing woman.

Paediatric use

To avoid liver damage due to overdose in infants and toddlers, dosing should be dependent on the clinical picture and the course of the disease.

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.

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.*

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.

Effect on laboratory tests

Erythromycin interferes with the fluorimetric determination of urinary catecholamines.

Effect on ability to drive and use machines

Erythromycin has a negligible influence on the ability to concentrate and react. However, the occurrence of undesirable effects can negatively influence the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

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 sub-therapeutic 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.

Oral anticoagulants:
There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants (e.g. warfarin) were used concomitantly.

Medicines that prolong the QTc interval:
Erythromycin has been shown to prolong the QTc interval and is associated with case reports of torsade de pointes in some patients. Patients with uncorrected electrolyte disorders particularly hypokalaemia, known prolongation of the QTc interval, or those concurrently receiving medicines that prolong the QTc interval, in particular Class IA (e.g. quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmics, certain neuroleptics, tri- and tetracyclic antidepressants, ebastine, arsenic trioxide, methadone, budipine, certain fluoroquinolones, imidazole antimycotics and anti-malarial drugs (e.g. pentamidin i.v.), are at increased risk of ventricular arrhythmias. As these predisposing conditions may increase the risk for ventricular arrhythmias, erythromycin should not be used in patients with ongoing proarrhythmic conditions (see **CONTRAINDICATIONS)**.

Medicines metabolised by the cytochrome P450 system:
Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome P450 system (CYP3A) and P-glycoprotein. Co-administration of erythromycin and a medicine primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic or adverse effects of the concomitant medicine e.g. ciclosporin, phenytoin, felodipine, hexobarbital, carbamazepine, alfentanil, disopyramide, bromocriptine, valproate, methylprednisolone, vinblastine, sildenafil, cilostazol, quinidine, tacrolimus rifabutin, verapamil, diltiazem, acenocoumarol, astemizole, digoxin, dihydroergotamine, ergotamine, midazolam, omeprazole, terfenadine, mizolastine, domperidone, theophylline, triazolam and antifungals (e.g. fluconazole, ketoconazole and itraconazole).

Dosage adjustments may be considered, and when possible, serum concentrations of medicines primarily metabolised by CYP3A4 should be monitored closely in patients receiving erythromycin.

Erythromycin has been shown to prolong the QTc interval and is associated with case reports of torsades de pointes in some patients. In one published study patients who used both oral erythromycin and strong CYP3A inhibitors (azole antifungal medicines [ketoconazole, itraconazole and fluconazole, all administered systemically], diltiazem, verapamil, troleandomycin, mibefradil, nefazodone) had a risk of sudden death from cardiac causes that was five times as great as that among patients who had not used these medicines. Many of the medicines that are known to block CYP3A4 also have direct effects on repolarisation, which may cause a dramatic lengthening of the QT interval. Given that there are alternatives to

erythromycin and these listed CYP3A inhibitors, the use of these combinations should be avoided.

Hypotension, bradyarrhythmia and lactic acidosis have been observed in patients receiving concurrent verapamil.

Medicines that induce CYP3A (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 after discontinuing treatment with CYP3A4 inducers. Erythromycin should not be used during, or for two weeks after stopping treatment, with CYP3A4 inducers.

The following are examples of some clinically significant CYP3A based drug interactions. Interactions with other medicines metabolised by the CYP3A isoform are also possible. The following CYP3A based drug interactions have been observed with erythromycin products in post-marketing experience:

Triazolobenzodiazepines (such as triazolam and alprazolam) and related benzodiazepines:
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**).

HMG-CoA reductase inhibitors:
Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g. lovastatin, simvastatin or atorvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these medicines concomitantly (see **CONTRAINDICATIONS**).

Sildenafil:
Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered.

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

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 (see **CONTRAINDICATIONS**).

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

Cimetidine:
It may inhibit the metabolism of erythromycin which may lead to an increased plasma concentration.

Protease inhibitors:
Protease inhibitors (e.g. ritonavir) has been reported to increase the level of effect of erythromycin by altering drug metabolism.

Anti-bacterial agents:
Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin and chloramphenicol. Same interaction is applicable with streptomycin, tetracyclines, colistin and bactericidal beta-lactam antibiotics (e.g. penicillin, cephalosporin).

ADVERSE EFFECTS

The most frequent adverse effects of erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose-related.

The following adverse effects have been reported for erythromycin. The adverse effects are listed according to the frequency defined as:

Very common (≥ 1/10)
Common (≥ 1/100 - <1/10)
Uncommon (≥ 1/1,000 - <1/100)
Rare (> 1/10,000 - <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Very common (≥ 1/10)	**Uncommon** (≥ 1/1,000 - < 1/100)	**Rare** (≥ 1/10,000 - < 1/1,000)	**Very rare** (< 1/10,000)	**Not known** (cannot be estimated from the available data)
Infections and infestations				
	Overgrowth of non-susceptible bacteria or fungi e.g. oral and vaginal candidosis	Pseudomembranous colitis		
Blood and lymphatic system disorders				
				Eosinophilia
Immune system disorders				

Very common (≥ 1/10)	**Uncommon** (≥ 1/1,000 - < 1/100)	**Rare** (≥ 1/10,000 - < 1/1,000)	**Very rare** (< 1/10,000)	**Not known** (cannot be estimated from the available data)
	Hypersensitivity ranging from urticaria and mild rash	Anaphylactic reaction including anaphylactic shock		
Metabolism and nutrition disorders				
Decreased appetite				
Psychiatric disorders				
				Hallucinations and confusional state
Nervous system disorders				
		Seizures		Headache, somnolence and dizziness
Eye disorders				
				Visual impairment including diplopia and vision blurred
Ear and labyrinth disorders				
			Tinnitus, reversible hearing loss and deafness*	Vertigo
Cardiac disorders				
		QT interval prolongation, cardiac arrhythmias, such as ventricular tachycardia (torsade de pointes), and palpitations.		
Vascular disorders				
				Hypotension
Respiratory, thoracic and mediastinal disorders				
				Dyspnoea (including asthmatic states)

Very common (≥ 1/10)	**Uncommon** (≥ 1/1,000 - < 1/100)	**Rare** (≥ 1/10,000 - < 1/1,000)	**Very rare** (< 1/10,000)	**Not known** (cannot be estimated from the available data)
Gastrointestinal disorders				
Nausea, vomiting, abdominal pain, flatulence, soft defecation or diarrhoea		Pancreatitis	Spastic hypertrophic pyloric stenosis in children	Abdominal discomfort
Hepatobiliary disorders				
	Elevation of certain liver enzymes (GPT, GOT, LDH, AP, γ-GT)	Cholestasis and Jaundice cholestatic	Hepatic dysfunction, with or without jaundice, hepatitis, and/or abnormal liver function test results, hepatomegaly and hepatic failure	
Skin and subcutaneous tissue disorders				
	Erythema, urticarial exanthema, pruritus	Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, Allergic oedema/angioedema		
Musculoskeletal and connective tissue disorders				
Muscle spasms		Joint swelling, Rhabdomyolysis	Unmasking and worsening of myasthenia gravis	
Renal and urinary disorders				
			Tubulointers-titial nephritis	

Very common (≥ 1/10)	Uncommon (≥ 1/1,000 - < 1/100)	Rare (≥ 1/10,000 - < 1/1,000)	Very rare (< 1/10,000)	Not known (cannot be estimated from the available data)
General disorders and administration site conditions				
		Pyrexia		Chest pain, malaise, headache

*These disorders are concentration-dependent and are more likely in patients with severe renal and/or hepatic impairment or in high doses or in cases of overdose.

Infantile hypertrophic pyloric stenosis (IHPS):
Seven 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.

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 ethyl succinate per day is required.

EES granules may be administered without regard to meals.

Adults

400 mg erythromycin (as ethyl succinate) 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:

Body Weight (kg)	Total Daily Dose
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

Special dosage recommendations

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 g 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 overdosage 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 on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

EES 200 mg/5 mL granules
Pink free flowing granules. When reconstituted with water to make 100 mL of 200 mg (erythromycin) per 5 mL, pink opaque cherry flavoured suspension in 100 mL HDPE bottles.

EES 400 mg/5 mL granules
Pink free flowing granules. When reconstituted with water to make 100 mL of 400 mg (erythromycin) per 5 mL, pink opaque cherry flavoured suspension in 100 mL HDPE bottles.

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

Amdipharm Mercury (Australia) Pty Ltd
Level 9, 76 Berry Street
North Sydney NSW 2060

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine – Schedule 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

200 mg/5 mL: 4 November 2010
400 mg/5 mL: 11 January 1996

DATE OF MOST RECENT AMENDMENT

24 July 2017

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