AUSTRALIAN PRODUCT INFORMATION

E-MYCIN®

(Erythromycin (as ethyl succinate)) film coated tablets and powder for oral liquid

1 NAME OF THE MEDICINE

Erythromycin (as ethyl succinate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of erythromycin (as ethyl succinate) as the active ingredient.

5 mL of granules when prepared contains either 200 mg or 400 mg of erythromycin (as ethyl succinate).

Excipients with known effect:

Tablets: contains sorbates.

Granules: contains benzoates, aspartame, phenylalanine and sorbitol.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

E-MYCIN tablet: 19mm X 8.7mm oval, normal convex, flesh pink film coated tablet marked "E-N" on one side, "alpha symbol" on the reverse

E-MYCIN 200 powder for oral liquid: Pink free flowing granules. When reconstituted, pink suspension with a cherry odour and flavour

E-MYCIN 400 powder for oral liquid: Pink free flowing granules. When reconstituted, pink suspension with a cherry odour and flavour

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Erythromycin is indicated for the treatment of the following infections:

Streptococcus pyogenes (group A β-haemolytic Streptococcus)

Upper and lower respiratory tract, skin and skin structure infections of mild to moderate severity.

When oral medication is given, patient must comply with the prescribed regimen. Therapeutic dose should be administered for at least 10 days.

α-haemolytic Streptococci (viridans group)

No controlled clinical efficacy trials have been conducted, however oral erythromycin has been suggested by the American Heart Association and the American Dental Association for use in bacterial endocarditis prophylaxis prior to dental/surgical procedures of the upper respiratory tract in penicillin-hypersensitive patients with a history of rheumatic, congenital or other acquired valvular heart disease. Erythromycin is not suitable prior to genitourinary or gastrointestinal tract surgery.

Staphylococcus aureus

Acute infections of skin and skin structure of mild to moderate severity. Bacterial resistance may emerge during treatment hence cultures and sensitivity tests should be performed.

Streptococcus pneumoniae (Diplococcus pneumoniae)

Upper (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 normally achieved.

Chlamydia trachomatis and Ureaplasma urealyticum

These organisms are sensitive to erythromycin; clinical studies have demonstrated erythromycin's efficacy in nongonococcal urethritis due to these organisms. A minimum of 10 days therapy is required.

Chlamydia trachomatis infection (excluding non-gonococcal urethritis)

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

Treponema pallidum

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

Neisseria gonorrhoeae

Erythromycin lactobionate for injection in conjunction with oral erythromycin ethyl succinate, as an alternative treatment for acute uncomplicated gonorrhoea in female patients with penicillin hypersensitivity. Before treatment, patients who are suspected of also having syphilis should be evaluated including a microscopic examination for T. pallidum (by immunofluorescence or darkfield) before receiving erythromycin, and monthly serologic tests should be performed for a minimum of 4 months.

Corynebacterium diphtheriae, C. minutissimum and 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; adjunctive therapy of moderate to severe acne.

Bordetella pertussis

For early elimination of the causative organism from the nasopharynx. Therapeutic doses should be continued for at least 10 days. The clinical course of the disease is not altered.

Clostridium tetani

In vitro, Clostridium tetani is sensitive to erythromycin. Erythromycin may be used prophylactically in penicillin-hypersensitive persons for 5 days. 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.

Campylobacter fetus (subspecies) jejuni, Listeria monocytogenes

Infections due to these organisms when antibiotic therapy is indicated.

4.2 DOSE AND METHOD OF ADMINISTRATION

E-MYCIN tablets and granules may be given without regard to meals.

The tablets are intended primarily for adult use. The granules are intended for constitution with water. When constituted, they are cherry-flavoured suspensions intended primarily for paediatric use but can also be used by adults.

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/day of erythromycin (as ethyl succinate) is required.

Adults

400 mg erythromycin every six hours is the usual dose. Dosage may be increased up to 4 g/day according to the severity of the infection.

If a twice daily dosage is desired, one-half of the total daily dose may be given every twelve hours, provided the daily dose does not exceed 1.6 g.

Children

Age, weight and severity of the infection are important factors in determining the proper dosage. In mild to moderate infections, the usual dosage for children 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, both for adults and children.

Bodyweight	Dose	Frequency	Daily dosage
23 to 45 kg	1 tablet (400 mg)	3 tablets/day	1,200 mg
Adults over 45 kg	1 tablet (400 mg)	4 tablets/day	1,600 mg

The total daily dosage must be administered in equally divided doses.

Granules. The recommended dosage ranges from 30 to 50 mg/kg/day or more in divided doses. For mild to moderately severe infections caused by erythromycin sensitive organisms, the following dosage schedule is suggested:

Bodyweight	Total Daily Dose
under 4.5 kg	30 to 50 mg/kg
4.5 to 6.8 kg	200 mg
6.8 to 11 kg	400 mg
11 to 23 kg	800 mg
23 to 45 kg	1,200 mg
over 45 kg	1,600 mg

The total daily oral dose may be given two, three or four times daily in equally divided portions.

The length of therapy will depend on the severity of the infection and other clinical factors.

For severe or life-threatening infections and infections of the lower respiratory tract, these doses may be doubled or increased even more. However, in such instances, it may be preferable to initiate treatment by the parenteral route with a suitable injectable preparation.

Special dosage recommendations

Treatment of streptococcal infections	A therapeutic dosage of erythromycin ethyl succinate should be administered for at least 10 days. In continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the usual dosage is 400 mg twice a day.
Used prior to dental or upper respiratory tract surgery to prevent endocarditis in patients at risk (see Section 4.1 THERAPEUTIC INDICATIONS, *α haemolytic Streptococci*)	A recommended schedule for adults is 1.6 g (20 mg/kg for children) 1.5 to 2 hours before the procedure and 800 mg every six hours for 6 doses after the procedure.
Treatment of primary syphilis	Adults: A total of 48 to 64 g given in divided doses over a period of 15 days.
Mycoplasmal and chlamydial infections	800 mg every six hours for a period of seven days, or alternatively 400 mg every six hours for 14 days.
Severe acne	400 mg four times daily for two weeks and then adjust the dose every 4 to 6 weeks, depending on clinical response. Therapy should be continued for at least three months.
Legionnaires' disease	Although optimal doses have not been established, doses utilised to date indicate a dosage of 0.8 to 1.6 g every six hours for 14 days.

4.3 CONTRAINDICATIONS

Erythromycin is contraindicated in the case of:

- Hypersensitivity to erythromycin, or any of the excipients in the formulation
- 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- 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, methadonem budipine, certain fluoroquinolones, imidazole anti-mycotics and anti-malarials (e.g. pentamidine i.v.) (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

- Concomitant use of simvastatin, lovastatin or atorvastatin. Treatment with these agents should be interrupted while taking erythromycin (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular events

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.

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.

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 Section 4.3 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.

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). The concomitant use of these medicines with erythromycin is contraindicated (see section 4.3 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 *Clostridium 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 may, however, begin up to several weeks to over two months after cessation of antibiotic therapy). This may be sufficient treatment in the early stages although colestyramine 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 *Clostridium difficile* should be considered.

Drugs 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.

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.

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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)), impairing the efficacy of this and other concomitantly taken medicines.

Use in Hepatic Impairment

There have been reports of hepatic dysfunction, including increased liver enzymes, hepatomegaly and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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 in contraindicated in severe hepatic impairment (see Section 4.3 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Use in the Elderly

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, QT prolongation.

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. A possible dose-response effect was described with an absolute risk of IHPS of 5.1% for infants who took erythromycin for 8 to 14 days and 10% for infants who took erythromycin for 15 to 21 days. 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 trachomatis*), 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 Laboratory Tests

Erythromycin interferes with the fluorimetric determination of urinary catecholamines.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Theophylline

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 cases 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.

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 anti-mycotics and anti-malarial medicines (e.g. pentamidine 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 Section 4.3 CONTRAINDICATIONS).

Erythromycin should also be used with caution in patients receiving Hydroxychloroquine and chloroquine which are also known to prolong the QT interval, due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

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 drug 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 (phenobarbitone), 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:

Corticosteroids

Caution should be exercised in concomitant use of erythromycin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

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 Section 4.3 CONTRAINDICATIONS).

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.

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 Section 4.3 CONTRAINDICATIONS).

Sildenafil (e.g. Viagra)

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

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.

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 torsades de pointes. Similar effects have been observed in patients taking pimozide and clarithromycin, another macrolide antibiotic. Concomitant administrations of erythromycin with cisapride or pimozide is contraindicated. (See Section 4.3 CONTRAINDICATIONS)

Zopiclone

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

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.

Fenofexadine

With concomitant administration, plasma concentrations of fexofenadine increase due to increased absorption

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).

4.6 FERTILITY, PREGNANCY AND LACTATION

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

Pregnancy Category: A

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 foetus 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 antibiotic, 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Paediatric Use), sensitisation or colonisation with fungi. Caution should therefore be exercised when erythromycin is administered to a breastfeeding woman.

4.7 EFFECTS 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

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 (≥ 1/1000 - < 1/100)
- Rare (> 1/10000 - < 1/1000)
- Very rare (< 1/10000)
- Not known (cannot be estimated from the available data)

Infections and infestations

Uncommon:	Overgrowth of non-susceptible bacteria or fungi (e.g. oral and vaginal candidiasis)
Rare:	Pseudomembranous colitis

*Fungal overgrowth in the oral cavity and genitalia may occur.

Blood and lymphatic system disorders

Not known:	Eosinophilia

Immune system disorders

Uncommon:	Hypersensitivity ranging from urticaria and mild rash
Rare:	Anaphylactic reaction including anaphylactic shock

Metabolism and nutritional disorders

Very common:	Decreased appetite

Psychiatric disorders

Not known:	Hallucinations and confusional state

Nervous system disorders

Rare:	Seizures
Not known:	Headache, somnolence and dizziness

Eye disorders

Not known:	Visual impairment including diplopia and vision blurred

Ear and labyrinth disorders

Very rare:	Tinnitus, reversible hearing loss and deafness*
Not known:	Vertigo

*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.

Cardiac disorders

Rare:	QT interval prolongation, cardiac arrhythmias such as ventricular tachycardia (torsade de pointes) and palpitations

Vascular disorders

Not known:	Hypotension

Respiratory, thoracic and mediastinal disorders

Not known:	Dyspnoea (including asthmatic states)

Gastrointestinal disorders

Very common:	Nausea, vomiting, abdominal pain, flatulence, soft defecation or diarrhoea

Rare:	Pancreatitis
Very rare:	Spastic hypertrophic pyloric stenosis in children
Not known:	Abdominal discomfort

Hepatobiliary disorders

Uncommon:	Elevation of certain liver enzymes (GPT, GPT. LDH, AP, γ-GT)
Rare:	Cholestasis and cholestatic jaundice
Very rare:	Hepatic dysfunction, with or without jaundice, hepatitis, and/or abnormal liver function test results, hepatomegaly and hepatic failure

Skin and subcutaneous tissue disorders

Uncommon:	Erythema, urticarial exanthema, pruritus
Rare:	Erythema multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, allergic oedema/angioedema
Not known:	Acute generalised exanthematous pustulosis (AGEP)

Musculoskeletal and connective tissue disorders

Very common:	Muscle spasms
Rare:	Joint swelling, rhabdomyolysis
Very rare:	Unmasking and worsening of myasthenia gravis

Renal and urinary disorders

Very rare:	Tubulointerstitial nephritis

General disorders and administration site conditions

Rare:	Pyrexia
Not known:	Chest pain, malaise, headache

Infantile Hypertrophic Pyloric Stenosis (IHPS)

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 oral erythromycin for pertussis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. The relative risk of IHPS was increased 6.8 fold (95% CI= 3-16) compared to a retrospective cohort of infants.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms: The ingestion of large amounts of erythromycin can be expected to cause hearing problems, gastrointestinal distress and other adverse effects (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Treatment: 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 peritoneal dialysis or haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Microbiology

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

Streptococcus pyogenes

α-haemolytic Streptococci (viridans group)

Staphylococcus aureus

Streptococcus pneumoniae

Corynebacterium diphtheriae (as an adjunct to antitoxin)

Corynebacterium minutissimum

Cutibacterium acnes (Propionibacterium)

Listeria monocytogenes

Neisseria gonorrhoeae

Haemophilus influenzae (some strains are resistant)

Bordetella pertussis (Whooping cough)

Legionella pneumophila

Treponema pallidum

Mycoplasma pneumoniae

Clostridium tetani

Chlamydia trachomatis

Chlamydophila pneumoniae and C. psittaci

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. Some strains of *Haemophilus influenzae* are resistant to erythromycin alone, but are susceptible when erythromycin and sulfonamides are administered concurrently. Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy.

Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin and chloramphenicol.

Susceptibility testing

Dilution or diffusion techniques – either quantitative (minimum inhibitory concentration [MIC]) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. Clinical and Laboratory Standards Institute (CLSI)).

Standardised susceptibility test procedures require the use of laboratory control organisms 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 the 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 inhabited 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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Erythromycin ethyl succinate is absorbed intact following oral administration, and undergoes hydrolysis to yield the active erythromycin base. Serum levels are comparable when administered to patients in either the fasting or non-fasting state. Individual peak serum levels are variable; the peak after each dose occurs in one to two hours.

Distribution

The extent of plasma protein binding is variable but is probably of the order of 75%. After absorption, 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 placental barrier, and foetal plasma levels are usually 5 to 20% of the maternal plasma concentration.

Excretion

In the presence of normal renal function, the plasma half-life is approximately 1.4 hours. In anuric patients, the half-life may increase to six hours, but dosage adjustment is not usually required. 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. 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. After oral administration, approximately 5% appears in the urine. A large proportion of the absorbed drug remains unaccounted for and is presumably metabolised, probably in the liver.

5.3 PRECLINICAL SAFETY DATA

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

E-MYCIN tablets contain calcium hydrogen phosphate, maize starch, sorbic acid, povidone, purified talc, sodium starch glycollate, magnesium stearate and Opadry Pink OY-B-34901 (ID 2963).

E-MYCIN granules contain sorbitol, propylene glycol alginate, sodium citrate dihydrate, aspartame, sodium benzoate, colloidal anhydrous silica, erythrosine and Trusil Nature Identical Dark Cherry Flavour 163837 (ID 11977).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

E-MYCIN:	Store tablets below 30°C.
E-MYCIN 200 and E-MYCIN 400:	Store granules below 25°C. Reconstituted suspension should be refrigerated at 2° - 8°C and used within 10 days; do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

E-MYCIN:	Pack type: HDPE bottle with a PP cap Pack size: 25 tablets
E-MYCIN 200 and E-MYCIN 400:	Pack type: HDPE bottle with a PP cap Pack size: 100 mL

Some strengths, pack sizes and/or pack types may not be marketed.

Reconstitution

Add 77 mL of water in small volumes and shake vigorously until no lumps are visible.

Refrigerate at 2° to 8°C.

Use within 10 days of date of preparation. Discard remaining portion thereafter. Shake well before use.

Australian Register of Therapeutic Goods (ARTG)

AUST R 71310 - E-MYCIN erythromycin 400mg (as ethyl succinate) tablet bottle

AUST R 48286 - E-MYCIN 200 erythromycin 200mg/5mL (as ethyl succinate) powder for oral liquid bottle

AUST R 48287- E-MYCIN 400 erythromycin 400mg/5mL (as ethyl succinate) powder for oral liquid bottle

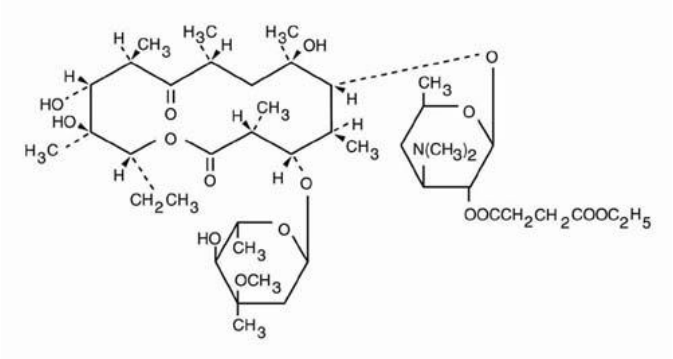
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is a base and readily forms salts with acids. The base, the stearate salt and the esters are poorly soluble in water. Erythromycin ethyl succinate is an ester of erythromycin suitable for oral administration.

Chemical Structure



Chemical name	4-(Dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy}-14-ethyl-7,12,13-trihydroxy-4--5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy}-3,5,7,9,11,13-hexamethyl-1-oxacyclotetradecane-2,10-dione
Molecular formula	$C_{43}H_{75}NO_{16}$
Molecular weight	862.05

CAS Number

1264-62-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

E-MYCIN 200 erythromycin 200 mg/5 mL (as ethyl succinate) powder for oral liquid bottle – 22/04/1994

E-MYCIN 400 erythromycin 400 mg/5 mL (as ethyl succinate) powder for oral liquid bottle – 22/04/1994

E-MYCIN erythromycin 400 mg (as ethyl succinate) tablet bottle – 07/10/1999

10 DATE OF REVISION

03/06/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes.
4.4	Added epidemiological risk data and risk-benefit guidance for cardiovascular events
5.1	Updated scientific names

E-MYCIN® is a Viatris company trade mark

E-MYCIN_pi\Jun26/00 (CCDS 06-Jan-2026)