

E-MYCIN

Erythromycin ethylsuccinate

Presentation

E-MYCIN 200: Granules for oral suspension. Free flowing pink granules which when mixed with the stated quantity of water provide a cherry flavoured suspension containing erythromycin ethylsuccinate 234 mg per 5 mL, equivalent to 200 mg per 5 mL of erythromycin.

E-MYCIN 400: Granules for oral suspension. Free flowing pink granules which when mixed with the stated quantity of water provide a cherry flavoured suspension containing erythromycin ethylsuccinate 468 mg per 5 mL, equivalent to 400 mg per 5 mL of erythromycin.

E-MYCIN TABLET: oval, normal convex, flesh pink coated tablet debossed "E-N" on one side and "α" on the other. Each tablet contains erythromycin ethylsuccinate 482 mg, equivalent to 400 mg of erythromycin.

Uses

Actions

Microbiology:

Erythromycin is a macrolide antibiotic that acts by inhibition of protein synthesis of the pathogen by binding 50S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vivo* between erythromycin and clindamycin, lincomycin and chloramphenicol.

Many strains of *Haemophilus influenzae* are resistant to erythromycin alone but are susceptible to erythromycin and sulphonamides together.

Staphylococci resistant to erythromycin may emerge during a course of therapy.

Erythromycin is usually active against most strains of the following organisms both *in vitro* and in clinical infections.

Gram-Positive Organisms:

Corynebacterium diphtheriae, *Corynebacterium minutissimum*, *Listeria monocytogenes*, *Staphylococcus aureus* (resistant organisms may emerge during treatment), *Streptococcus pneumoniae*, *Streptococcus pyogenes*.

Gram-Negative Organisms:

Bordetella pertussis, *Legionella pneumophila*, *Neisseria gonorrhoeae*.

Other Micro-Organisms:

Chlamydia trachomatis, *Entamoeba histolytica*, *Mycoplasma pneumoniae*, *Ureaplasma urealyticum*.

Erythromycin has been shown to be active *in vitro* against most strains of the following organisms; however, the safety and efficacy of erythromycin in treating infections due to these organisms have not been established in adequate and well-controlled trials:

Gram-Positive Organisms:

Alpha haemolytic streptococci (viridans group).

Gram-Negative Organisms:

Moraxella (Branhamella) catarrhalis.

Other Micro-Organisms:

Entamoeba histolytica, *Treponema pallidum*.

Not all strains of the organism 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 alone but are susceptible to erythromycin and sulphonamides together.

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.

Pharmacokinetics

Orally administered erythromycin ethylsuccinate tablets and suspension are readily and reliably absorbed. Comparable levels of erythromycin are achieved in the fasting and nonfasting states.

Erythromycin diffuses readily into most body fluids. Only low concentrations are normally achieved in the spinal fluid, but passage of the medicine across the blood-brain barrier increases in meningitis. In the presence of normal hepatic function erythromycin is concentrated in the liver and excreted in the bile. The effect of hepatic dysfunction on excretion of erythromycin by the liver into the bile is not known. Less than 5 percent of the orally administered dose is excreted in active form in the urine.

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 streptococcal pharyngitis and in long term prophylaxis of rheumatic fever, erythromycin is an alternate drug 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.

Prevention of Initial Attacks of Rheumatic Fever:

Penicillin is considered to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of Group A beta-haemolytic streptococcal infections of the upper respiratory tract e.g.

tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients. The therapeutic dose should be administered for 10 days.

Prevention of Recurrent Attacks of Rheumatic Fever:

Penicillin or sulphonamides are considered to be the drugs of choice in the prevention of recurrent attacks of rheumatic fever. In patients who are allergic to penicillin and sulphonamides, oral erythromycin is recommended in the long term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).

Prevention of Bacterial Endocarditis:

Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been recommended for prevention of bacterial endocarditis in penicillin-allergic patients with prosthetic cardiac valves, most congenital cardiac malformations, surgically constructed systemic pulmonary shunts, rheumatic or other acquired valvular dysfunction, idiopathic hypertrophic subaortic stenosis (IHSS), previous history of bacterial endocarditis or mitral valve prolapse with insufficiency when they undergo dental procedures or surgical procedures of the upper respiratory tract.

Alpha-haemolytic streptococci (viridans group):

Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been suggested 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 procedures 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. 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 to erythromycin at concentrations achieved with usual therapeutic doses; resistant strains may require concomitant therapy with sulphonamides.

Ureaplasma urealyticum:

For the treatment of urethritis caused by these organisms in adult males.

Neisseria gonorrhoeae:

ERA-IV (erythromycin lactobionate for injection) in conjunction with erythromycin orally, as an alternative drug in treatment of acute pelvic inflammatory disease caused by *N. gonorrhoeae* in female patients with a history of sensitivity to penicillin. Before treatment of gonorrhoea, patients who are suspected of also having syphilis should have a microscopic examination for *T. pallidum* (by immunofluorescence or darkfield) before receiving erythromycin, and monthly serologic tests for a minimum of 4 months thereafter.

Chlamydia trachomatis:

Erythromycin is indicated for treatment of the following infections caused by *Chlamydia trachomatis*; conjunctivitis of the newborn, pneumonia of infancy and urogenital infections during pregnancy (see Warnings and Precautions). When tetracyclines are contraindicated or not tolerated, erythromycin is

indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults due to *Chlamydia trachomatis*.

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 therapy. Erythromycin should not be used for the treatment of syphilis in pregnancy because it cannot be relied upon to cure an infected foetus.

Corynebacterium diphtheriae:

As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

Corynebacterium minutissimum:

For the treatment of erythrasma.

Entamoeba histolytica:

In treatment of intestinal amoebiasis only. Extra-enteric amoebiasis requires treatment with other agents.

Listeria monocytogenes:

Infections due to this organism.

Bordetella pertussis:

Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Legionnaire's Disease:

Clinical evidence suggests that erythromycin is the preferred antibiotic for treating Legionnaire's Disease.

Dosage and Administration

E-Mycin suspensions and tablets may be administered without regard to meals.

Children:

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

If twice-a-day dosage is desired one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily if desired by administering one-third of the total daily dose every 8 hours.

The following dosage schedule is suggested for mild to moderate infections

Body weight	Total daily dose (erythromycin base)
<4.5kg	30-50 mg/kg/day
4.5 - 6.8kg	200 mg

6.8 - 11.3kg	400 mg
11.3 – 22.7kg	800 mg
22.7 - 45.4kg	1200 mg
Over 45.4kg	1600 mg

Adults:

400 mg erythromycin (as erythromycin ethylsuccinate) every 6 hours is the usual dose. Dosage may be increased up to 4 g per day according to the severity of the infection. If twice-a-day dosage is desired, one-half of the total daily dose may be given every 12 hours. Doses may also be given three times daily by administering one-third of the total daily dose every 8 hours.

In the treatment of streptococcal infections, a therapeutic dosage of erythromycin (as erythromycin ethylsuccinate) 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.

For prophylaxis against bacterial endocarditis in patients with congenital heart disease, or rheumatic or other acquired valvular heart disease when undergoing dental procedures or surgical procedures of the upper respiratory tract, give 1.6 g (20 mg/kg for children) orally 1.5 to 2 hours before the procedure, and then 800 mg (10 mg/kg for children) orally every 6 hours for 8 doses.

For treatment of urethritis due to *C. trachomatis* or *U. urealyticum* 800 mg every 6 to 8 hours for 7 days or 400 mg every 6 to 8 hours for 14 days.

For treatment of primary syphilis: Adults 48 to 64 g given in divided doses over a period of 10 to 15 days.

For intestinal amoebiasis: Adults 400 mg four times daily for 10 to 14 days. Children 30 to 50 mg/kg/day in divided doses for 10 to 14 days.

For use in pertussis: Although optimal dosage and duration have not been established, doses of erythromycin utilized in reported clinical studies were 40 to 50 mg/kg/day, given in divided doses for 5 to 14 days.

For treatment of Legionnaire's Disease: Although optimal doses have not been established, doses utilized in reported clinical data were 1.6 to 4 g daily in divided doses.

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.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, cisapride, pimozide, and ergotamine or dihydroergotamine (see Interactions).

Warnings and Precautions

Hepatic dysfunction, including increased liver enzymes and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with erythromycin. As erythromycin is principally excreted by the liver, caution should be exercised when administering erythromycin to patients with impaired liver function.

There have been reports suggesting erythromycin does not reach the foetus in adequate concentrations to prevent congenital syphilis. Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen.

Pseudomembranous colitis has been reported with most antibacterial agents, including erythromycin. Therefore, it is important to consider this diagnosis in patients who develop diarrhoea in association with antibiotic use.

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.

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

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.

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

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. Patients should be informed to contact their physician if vomiting or irritability with feeding occurs.

Carcinogenesis:

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

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*.

Impairment of 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 maximum human dose).

Pregnancy:

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 were 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 foetal plasma levels are generally low.

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

Use in Lactation:

Erythromycin appears in breast milk. It is not known whether it can harm the nursing child. The expected benefits and the potential hazards should be carefully assessed.

Laboratory Tests:

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Adverse Effects

The most frequent side effects of erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhoea and anorexia.

Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur (see Warnings and Precautions).

Pseudomembranous colitis has been rarely reported in association with erythromycin therapy.

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 rarely been reported.

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

As with other macrolides, QT prolongation, ventricular tachycardia and torsades de pointes have been rarely reported with erythromycin.

There have been isolated reports of transient central nervous system side effects including seizures, hallucinations, confusion, vertigo, and tinnitus; 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.

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 case of theophylline

toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

There have been published reports suggesting when erythromycin is given concomitantly with theophylline there is a significant decrease in erythromycin serum concentrations. This could result in subtherapeutic concentrations of erythromycin.

Digoxin:

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

Anticoagulants:

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

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

Erythromycin has been reported to decrease the clearance of triazolam, and midazolam, and thus may increase the pharmacologic effect of these benzodiazepines.

Drugs metabolised by the cytochrome P450:

The use of erythromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, phenytoin, alfentanil, disopyramide, bromocriptine, valproate, tacrolimus, quinidine, methylprednisolone, cilostazol, vinblastine, sildenafil, terfenadine, astemizole and rifabutin. Serum concentrations of drugs metabolised by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Terfenadine:

Erythromycin significantly alters the metabolism of terfenadine when taken concomitantly. Rare cases of serious cardiovascular adverse events including death, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed (see Contraindications and Adverse Effects).

Zopiclone:

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

Astemizole:

Erythromycin significantly alters the metabolism of astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events including cardiac arrest, torsade de pointes, and other ventricular arrhythmias have been observed (see Contraindications and Adverse Effects).

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.

Ergotamine / dihydroergotamine:

Post-marketing reports indicate that co-administration of erythromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm and ischemia of the extremities and other tissues including the central nervous system (see Contraindications).

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). In case of overdosage, erythromycin should be discontinued. 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 0800 764 766.

Pharmaceutical Precautions

Store tablets and granules below 30°C. Reconstituted suspension should be refrigerated and used within 10 days; do not freeze.

Medicine Classification

Prescription Medicine.

Package Quantities

E-MYCIN 200: Granules for oral suspension 100 mL. Reconstituted suspension contains erythromycin ethylsuccinate equivalent to 200 mg per 5 mL of erythromycin.

E-MYCIN 400: Granules for oral suspension 100 mL. Reconstituted suspension contains erythromycin ethylsuccinate equivalent to 400 mg per 5 mL of erythromycin.

E-MYCIN TABLETS: 100 film coated tablets each containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin.

Further Information

List of Excipients

E-MYCIN tablets

The E-Mycin tablets contain calcium hydrogen phosphate anhydrous, maize starch, sorbic acid, povidone, purified talc, sodium starch glycollate, magnesium stearate and Opadry Pink OY-B-34901 (contains the colours titanium dioxide and iron oxide red).

E-Mycin tablets do not contain lactose or gluten.

E-MYCIN mixtures

E-Mycin granules contain sorbitol, sodium citrate dihydrate, aspartame, propylene glycol alginate, silicon dioxide colloidal, sodium benzoate, erythrosine CI45430, Trusil Nature Identical Cherry Flavour (contains preservative 320 and less than 0.011% gluten).

E-Mycin mixtures do not contain lactose.

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