Prescribing Information

Pr ERYBID®
(erythromycin tablets)
500 mg Dispertab® tablets

Pr EES®-200/400
(erythromycin ethylsuccinate oral suspension USP)
200 or 400 mg erythromycin activity/5 mL

Pr PCE®
(erythromycin tablets)
333 mg Dispertab® tablets

Therapeutic Classification

Antibiotic

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PRESCRIBING INFORMATION

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THERAPEUTIC CLASSIFICATION

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ACTION AND CLINICAL PHARMACOLOGY

Erythromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible bacteria and suppressing protein synthesis. Erythromycin is usually bacteriostatic but may be bactericidal in high concentrations or against highly susceptible organisms. Orally administered erythromycin base and its salts are absorbed in the microbiologically active form. Significant inter-individual variations in the absorption of erythromycin were observed and some patients do not achieve maximal serum levels.

Erythromycin is largely bound to plasma proteins (over 70%).

In the presence of normal hepatic function, erythromycin is concentrated in the liver and is excreted in the bile; the effect of hepatic dysfunction on biliary excretion of erythromycin is not known.

Erythromycin diffuses readily into most body fluids. Only low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis.

From 12 to 15 percent of intravenously administered erythromycin is excreted in active form in the urine. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine.

The half-life ($t_{1/½}$) for erythromycin is approximately 2 hours.

Microbiology

Many strains of *Hemophilus influenzae* are resistant to erythromycin alone.

Staphylococci resistant to erythromycin may emerge during a course of erythromycin therapy. Culture and sensitivity testing should be performed prior to and during therapy.

Erythromycin is usually bacteriostatic but may be bactericidal in high concentrations. The bactericidal activity is greatest against a small number of rapidly dividing microorganisms and increases markedly as the pH of the medium is raised over the range of pH 5.5 to 8.5.

Susceptibility Testing

The standard single disc susceptibility test (using the 15 µg erythromycin disc) and the dilution susceptibility test should be interpreted according to the criteria in Table 1.

Table 1
Criteria for Interpreting Standard Single Disc Susceptibility Test and The Dilution Susceptibility Test

	Zone Diameter (mm)	Approximate MIC Correlate (mg/L)
Susceptible	. 23	. 0.5
Intermediate*	14-22	1-4
Resistant	. 13	. 8

* Indicates that the test results are equivocal; therefore, dilution tests may be indicated.
N.B.: These criteria and the definition are in agreement with NCCLS Order Code M2A3.

Control limits for monitoring erythromycin susceptibility tests are given in Table 2.

Table 2
Control Limits for Monitoring Erythromycin Susceptibility Tests

	Zone Diameter (mm)	MIC (mg/L)
S. aureus ATCC 29213	22-30	0.12 - 0.50
S. faecalis ATCC 29212		1.0 - 4.0

INDICATIONS AND CLINICAL USES

All erythromycins (base, salt and esters) have the same spectrum of antimicrobial activity. Erythromycin is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

1. Upper respiratory tract infections of mild to moderate severity caused by *S. pyogenes* (Group A beta-hemolytic streptococci), *S. pneumoniae* and *H. influenzae*.

   N.B. Not all strains of *H. influenzae* are susceptible to erythromycin at the concentrations of the antibiotic achieved with usual therapeutic doses.

2. Lower respiratory tract infections of mild to moderate severity caused by *S. pyogenes* (Group A beta-hemolytic streptococci), *S. pneumoniae* and *Mycoplasma pneumoniae*.

3. Skin and soft tissue infections of mild to moderate severity caused by *S. pyogenes* and *S. aureus*.

   N.B. Resistance of staphylococci may emerge during treatment.

4. Primary syphilis caused by *T. pallidum*. Erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to penicillins. Spinal fluid examinations should be performed before treatment and as part of the post-therapy follow-up. Erythromycin should not be used for the treatment of syphilis in pregnancy because it cannot be relied upon to cure an infected fetus.

5. Diphtheria caused by *C. diphtheriae*. As an adjunct to antitoxin, to prevent the establishment of carriers, and to eradicate the organisms in carriers.

6. Erythrasma caused by *C. minutissimum*.

7. Pertussis caused by *B. pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them non-infectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

8. Legionnaires' disease caused by *L. pneumophila*. Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited clinical data suggest that erythromycin can be effective in treating Legionnaires' disease.

9. Chlamydial Infections: The 1992 "Canadian Guidelines for the Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults" recommends erythromycin for the treatment of the following infections when caused by *Chlamydia trachomatis*:

   a. In newborns and infants for conjunctivitis and pneumonia.

      N.B. Topical therapy alone for conjunctivitis is NOT adequate.

b. In children under 9 years of age, in pregnant women and in nursing mothers for uncomplicated urethral, endocervical or rectal infection.

c. In adolescents and adults, when tetracycline or doxycycline is contraindicated or not tolerated, for uncomplicated urethral, endocervical or rectal infection.

10. The treatment of acne vulgaris.

11. Erythromycin should not be used for the treatment of syphilis in pregnancy because it cannot be relied upon to cure an infected fetus (see **PRECAUTIONS, Pregnancy**).

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify the causative organisms and to determine their susceptibility to erythromycin. Therapy may be instituted before results of susceptibility studies are known; however, antibiotic treatment should be re-evaluated when the results become available or if the clinical response is not adequate.

Prophylaxis

For prophylaxis against bacterial endocarditis (alpha-hemolytic streptococci) in penicillin-allergic patients who have congenital heart disease or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract. Erythromycin is not suitable for prophylaxis prior to genitourinary or gastrointestinal tract surgery.

Penicillin or sulfonamides 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 sulfonamides, oral erythromycin is recommended in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).

CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to erythromycin, clarithromycin or other macrolide antibacterial agents. Erythromycin is also contraindicated as concurrent therapy with astemizole*, terfenadine*, cisapride*, pimozide, and ergotamine or dihydroergotamine (see **PRECAUTIONS**: **Drug Interactions**).

WARNINGS

Erythromycin should be administered with caution to any patient who has demonstrated some form of allergy to drugs. If an allergic reaction to erythromycin occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require epinephrine, antihistamines, or corticosteroids.

Hepatic dysfunction, including increased liver enzymes and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with erythromycin. If findings

* Astemizole, terfenadine and cisapride are no longer marketed in Canada.

suggestive of significant hepatic dysfunction occur, therapy with erythromycin products should be discontinued.

Pseudomembranous colitis has been occasionally reported to occur in association with erythromycin therapy, and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients administered erythromycin who develop diarrhea. Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. If the colitis is not relieved by discontinuation of erythromycin administration or when it is severe, consideration should be given to the administration of vancomycin or other suitable therapy. Other possible causes of the colitis should also be considered.

There have been reports suggesting erythromycin does not reach the fetus 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.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin.

PRECAUTIONS

Prolonged or repeated use of erythromycin may result in an overgrowth of non-susceptible bacteria or fungi and organisms initially sensitive to erythromycin. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function.

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

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.

Drug Interactions

Terfenadine

Terfenadine undergoes metabolism in the liver by a specific cytochrome P450 isoenzyme. This metabolic pathway may be impaired in patients who are taking erythromycin, an inhibitor of this isoenzyme. Interference with this enzyme can lead to elevated terfenadine plasma levels which may be associated with QT prolongation. Rare cases of serious cardiovascular adverse events including death, cardiac arrest, torsades de pointes and other ventricular arrhythmias (such as

ventricular tachycardia, and ventricular fibrillation) have been observed (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Astemizole

Concomitant administration of astemizole with erythromycin is contraindicated because erythromycin is known to impair the Cytochrome P450 enzyme system which also influences astemizole metabolism. 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 REACTIONS**).

Cisapride / Pimozide

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 with concomitant administration of pimozide and clarithromycin, another macrolide antibiotic.

Theophylline

Recent data from studies of erythromycin in patients reveal that its 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 that when oral erythromycin is given concurrently with theophylline, there is a significant decrease in erythromycin serum concentrations. This decrease could result in subtherapeutic concentrations of erythromycin.

Lincomycin / Clindamycin / Chloramphenicol

Erythromycin should be used with caution if administered concomitantly with these drugs. *In vitro* experiments have demonstrated that binding sites for erythromycin, lincomycin, clindamycin and chloramphenicol overlap and competitive inhibition may occur.

Carbamazepine / Cyclosporin / Hexobarbital / Phenytoin / Alfentanil / Disopyramide / Bromocriptine / Valproate / Terfenadine / Astemizole / Tacrolimus / Quinidine / Methylprednisolone / Cilostazol / Vinblastine / Sildenafil / Rifabutin

Concomitant administration of erythromycin with drugs metabolized by the cytochrome P450 such as carbamazepine, cyclosporin, hexobarbital, phenytoin, alfentanil, disopyramide, bromocriptine, valproate, terfenadine, astemizole, tacrolimus, quinidine, methylprednisolone, cilostazol, vinblastine, sildenafil, and rifabutin have been reported to result in elevated plasma levels of these agents, leading to toxicity in some patients.

Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Oral Anticoagulants

Published reports indicate that caution should be observed when erythromycin and oral anticoagulants are used concurrently since prothrombin time may be prolonged.

Triazolobenzodiazepines (such as triazolam and alprazolam) and related benzodiazepines

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

Ergotamine / Dihydroergotamine

There are reports that ischemic reactions may occur when erythromycin is given concurrently with ergotamine-containing drugs.

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

Digoxin

There have been reports that there is a rise in plasma digoxin levels during concomitant administration of erythromycin.

HMG-CoA Reductase Inhibitors

Erythromycin has been reported to increased concentrations of HMG-CoA Reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking erythromycin concomitantly with HMG-CoA Reductase inhibitors.

Colchicine

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

Alfentanil

The concomitant use of erythromycin with alfentanil can significantly inhibit the clearance of alfentanil and may increase the risk of prolonged or delayed respiratory depression.

Zopiclone

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

Laboratory Tests

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term (two-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 tumorigenicity. Mutagenicity studies conducted did not show any genotoxic potential, and there was no apparent effect on male or female fertility in rats treated with erythromycin base by oral gavage at 700 mg/kg/day.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. However, observational studies in humans have reported cardiovascular malformations after exposure to medicinal products containing erythromycin during early pregnancy.

Erythromycin should not be used by women during pregnancy unless clearly needed.

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

No evidence of teratogenecity or embryotoxicity was observed in the following studies in animals:

Reproductive toxicity in rats with 350 mg/kg/day (7 times the human dose) and 700 mg/kg/day (14 times the human dose) of erythromycin base prior to and during mating, during gestation, and through weaning.

Reproductive toxicity in Swiss Webster mice with 700 mg/kg/day (14 times the human dose) of erythromycin base during the period of embryo-fetal organogenesis (gestational day 6-15).

Labour and Delivery

The effect of erythromycin on labour and delivery is unknown.

Nursing mothers

The safety of erythromycin for use during breast feeding has not been established. Erythromycin is excreted in breast milk.

Neonates

The safety of erythromycin for use in neonates has not been established.

Pediatric Use

See DOSAGE AND ADMINISTRATION

ADVERSE REACTIONS

Gastrointestinal Abdominal cramping, discomfort. Nausea, vomiting, diarrhea, and anorexia are also observed but less frequently. Pseudomembranous colitis has been occasionally reported to occur in association with erythromycin therapy (see WARNINGS).

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

Pancreatitis There have been rare reports of pancreatitis. There has also been a report of a case of erythromycin-induced pancreatitis following erythromycin overdose.

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

Cardiovascular Occasional case reports of cardiac arrhythmias such as ventricular tachycardia have been documented in patients receiving erythromycin therapy. There have been isolated reports of other cardiovascular symptoms such as chest pain, dizziness, and palpitations; however, a cause and effect relationship has not been established. As with other macrolides, QT prolongation, ventricular tachycardia, and Torsades de Pointes have been rarely reported with erythromycin (see CONTRAINDICATIONS).

Neurological Central nervous system side effects including seizures, hallucinations, confusion, vertigo and tinnitus have been reported occasionally in patients; however, a cause and effect relationship has not been established. There have also been rare reports of convulsions.

Miscellaneous During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi and organisms initially sensitive to erythromycin (e.g. *Staphylococcus aureus*, *Hemophilus influenzae*). If such infections occur, erythromycin should be discontinued and appropriate therapy instituted.

Occasionally there have been reports of reversible hearing occurring chiefly in patients with renal insufficiency and patients receiving high doses of erythromycin.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Following oral doses of over 2 g/day, abdominal discomfort, nausea or diarrhea may occur. Recently there has been a report of a case of erythromycin-induced pancreatitis following erythromycin overdose.

Treatment

There is no specific treatment for overdosage. The administration of erythromycin should be discontinued and gastric lavage considered, if appropriate; otherwise, the treatment should be symptomatic.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

TREATMENT

Administration - Adults

PCE® 333 mg tablets should be administered three times a day. Maximum blood levels are obtained when PCE is given to the fasting state (½ hour and preferably 2 hours before meals).

ERYBID®: 500 mg every 12 hours. Maximum blood levels are obtained when ERYBID is given in the fasting state (½ hour and preferably 2 hours before meals).

For severe infections: Up to 4 g of erythromycin (all forms) may be given daily in divided doses. These larger doses (eg. 4 g daily) are necessary for the treatment of known or suspected Legionella infections.

Administration - Children

EES® 200/400: Age, weight, and severity of the infection are important factors in determining the proper dosage. The recommended dosage is 30 to 50 mg/kg/day of erythromycin in three equally divided doses regardless of meals. For severe infections: The dose may be doubled. However, maximum blood levels are obtained when EES® is given immediately after meals.

For Group A streptococcal infections, therapy should be continued for at least 10 days.

Chlamydial Infections

The 1992 "Canadian Guidelines for the Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults" recommends the following doses of erythromycin:

1. Conjunctivitis and pneumonia in newborns and infants:

During first week of life:
infants < 2000 g: 20 mg/kg/day orally in divided doses
infants > 2000 g: 30 mg/kg/day orally in divided doses
> 1 week or 1 month: 40 mg/kg/day orally in divided doses.

The above regimens should be given for at least 14 days.

N.B. Topical therapy alone for conjunctivitis is **NOT** adequate.

2. Uncomplicated urethral, endocervical or rectal infection:

   a) Children under 9 years of age; 40 mg/kg/day orally in four divided doses (up to a maximum of 500 mg q.i.d. for 7 days).

   b) Children over 9 years of age when tetracycline or doxycycline is contraindicated or not tolerated: 40 mg/kg/day orally in four divided doses (up to a maximum of 500 mg q.i.d. for 7 days).

   c) Pregnant women and nursing mothers: 500 mg orally q.i.d. for 7 days or 250 mg orally q.i.d. for 14 days if the larger dose is not tolerated.

   d) Adolescents and adults when tetracycline or doxycycline is contraindicated or not tolerated: 500 mg q.i.d. for 7 days.

3. Complicated infection: the duration of treatment should be for at least 10 days.

As with all sexually transmitted diseases, follow up cultures after termination of therapy are recommended in order to assess the microbiological response.

Acne vulgaris

Initially up to one gram per day in divided doses. Depending on clinical response, this may then be reduced to 333 to 500 mg per day as a maintenance dose. Extended administration of erythromycin requires regular evaluation, particularly of liver function.

PROPHYLAXIS

Adults

For prophylaxis against bacterial endocarditis due to alpha-hemolytic streptococci in penicillin-allergic 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, the adult dose is 1 g orally 2 hours prior to the procedure, and then 500 mg orally 6 hours later.

For continuous prophylaxis against recurrences of streptococcal infections in persons with a well established history of rheumatic fever and clinical rheumatic heart disease, the dose is 250 mg twice a day.

Note: The doses are expressed in terms of erythromycin base.

See PRECAUTIONS regarding Alfentanil.

Children

For prophylaxis against bacterial endocarditis due to alpha-hemolytic streptococci in penicillin-allergic 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, the pediatric dose is 20 mg/kg (maximum 1 g) 2 hours before surgery followed by 10 mg/kg (maximum 500 mg) 6 hours later.

See PRECAUTIONS regarding Alfentanil.

AVAILABILITY OF DOSAGE FORM

ERYBID®:

ERYBID® (erythromycin tablets) is supplied in bottles of 100, 250 and 500 ovaloid white Dispertab® tablets containing 500 mg of erythromycin base. Also contains lactose. Alcohol-, gluten-, paraben-, sucrose-, sulfite- and tartrazine-free.

Store between 15 and 25°C.

PCE®

PCE® (erythromycin tablets) is supplied in bottles of 100, 250 and 500 ovaloid pink-speckled white Dispertab® tablets containing 333 mg of erythromycin base. Also contains lactose. Alcohol-, gluten-, paraben-, sodium-, sucrose-, sulfite- and tartrazine-free.

Store between 15 and 25°C.

EES®

EES® 200: Each 5 mL of reconstituted banana-flavoured suspension contains erythromycin ehtylsuccinate equivalent to 200 mg of erythromycin activity. Also contains sucrose. Alcohol-, gluten-, lactose-, paraben-, sulfite- and tartrazine-free. Store granules between 15 and 25°C.

EES® 400: Each 5 mL of reconstituted banana-flavoured suspension contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin activity. Also contains sucrose. Alcohol-, gluten-, lactose-, paraben-, sulfite- and tartrazine-free. Store granules between 15 and 25°C.

EES Granules come in a 7 or 10-day MEM PAC® containing 105 mL or 150 mL bottles for 7 or 10-day treatment.