

PRESCRIBING INFORMATION

^{PR}ERYTHRO-BASE

Erythromycin (base) Tablets USP

250 mg

^{PR}ERYTHRO E-C

Erythromycin (base) Delayed-Release Capsules

House Standard

250 mg and 333 mg

Antibiotic

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

Erythromycin exerts its antibacterial action by binding with the 50S ribosomal subunit of the organism, inhibiting peptide bond formation and protein synthesis within the bacterial cell. The activity is bacteriostatic or bactericidal depending on concentration.

INDICATIONS AND CLINICAL USE

Erythromycin is indicated for the treatment of the following infections caused by susceptible strains of the designated microorganisms:

- **Upper Respiratory Tract Infections:** those of mild to moderate severity caused by *Streptococcus pyogenes* (group A beta-hemolytic streptococci); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); and *Hemophilus influenzae*. Not all strains of *Hemophilus influenzae* are susceptible to erythromycin with usual therapeutic doses.
- **Lower Respiratory Tract Infections:** those of mild to moderate severity when caused by *Streptococcus pyogenes* (group A beta-hemolytic streptococci); *Streptococcus pneumoniae* (*Diplococcus pneumoniae*); and *Mycoplasma pneumoniae* (Eaton's agent).

Pertussis (Whooping Cough): caused by *Bordetella pertussis*. Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them noninfectious. Clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Diphtheria: As an adjunct to antitoxin in infections due to *Corynebacterium diphtheriae*, to prevent establishment of carriers and to eradicate the organism in carriers.

Legionnaires' Disease: caused by *Legionella pneumophila*. Controlled clinical efficacy studies have not been conducted. In vitro and limited preliminary clinical data suggest that erythromycin can be effective in the treatment of Legionnaires' disease.

- **Skin and Soft Tissue Infections:** those of mild to moderate severity when caused by *Streptococcus pyogenes* and *Staphylococcus aureus* (resistance of staphylococci may emerge during treatment).

Erythrasma: in the treatment of infections due to *Corynebacterium minutissimum*.

The treatment of *Acne vulgaris*.

- **Sexually Transmitted Diseases:**

Primary Syphilis: caused by *Treponema pallidum*. Erythromycin is an alternate choice for treatment for primary syphilis in patients allergic to the penicillins. Spinal fluid should be examined before treatment and as part of the follow-up after therapy.

Chlamydia Trachomatis Infection: Erythromycin is an alternate choice in the treatment of the following infections when caused by *Chlamydia trachomatis*:

- a) In infants and children (9 years and older) for conjunctivitis.
NOTE: Topical therapy alone for conjunctivitis is NOT adequate.
- b) In pregnant women and nursing mothers for urethral, endocervical or rectal infections.
- c) In youths and adults, for urethral, endocervical or rectal infections.

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.

CONTRAINDICATIONS

Erythromycin should not be used in patients with known hypersensitivity to erythromycin or the product's components, with infections caused by microorganisms that are resistant to the drug.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozone, ergotamine, dihydroergotamine or cisapride. There have been post-marketing reports of drug interactions when erythromycin is co-administered with cisapride, astemizole, pimozone or terfenadine resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes) most likely due to inhibition of hepatic metabolism of these drugs by erythromycin. Fatalities have been reported (see PRECAUTIONS, Drug Interactions).

WARNINGS

QT prolongation, ventricular tachycardia, and torsades de pointes have been reported with macrolides, including erythromycin (see ADVERSE EFFECTS, CONTRAINDICATIONS and PRECAUTIONS, Drug Interactions).

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.

Infants born to women treated during pregnancy with oral erythromycin for early syphilis should be treated with an appropriate penicillin regimen since erythromycin does not reach the fetus in adequate concentration.

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin products, particularly erythromycin estolate. If findings suggestive of significant hepatic dysfunction occur, therapy with erythromycin products should be discontinued.

***Clostridium difficile*-associated disease (CDAD):**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including erythromycin. CDAD may range in severity from mild diarrhoea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhoea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be

instituted as clinically indicated, as surgical intervention may be required in certain severe cases. (see ADVERSE EFFECTS).

The risk of myopathy during treatment with certain HMGCoA reductase inhibitors is increased with concomitant administration of erythromycin. Physicians considering combined therapy should carefully weigh the potential benefits and risks and monitor patients for any signs and symptoms of muscle pain, tenderness or weakness. (See PRECAUTIONS, Drug Interactions).

PRECAUTIONS

General

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.

Exacerbation of symptoms of myasthenia gravis and new onset of symptoms of myasthenic syndrome has been reported in patients receiving erythromycin therapy.

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

Laboratory Tests: Erythromycin interferes with the fluorometric determination of urinary catecholamines.

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, and increased risk of ventricular tachyarrhythmias (such as torsades de pointes, ventricular tachycardia, and ventricular fibrillation). (see CONTRAINDICATIONS).

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. There have been two reports to date of syncope with torsades de pointes requiring hospitalization in patients taking astemizole with erythromycin. In each case the QT intervals were prolonged beyond 650 milliseconds at the time of the event; one patient also received ketoconazole and the other patient also had hypokalemia. (see CONTRAINDICATIONS).

Rare cases of serious cardiovascular adverse events, including death, cardiac arrest and other ventricular arrhythmias have been observed.

Theophylline: The concomitant administration of erythromycin and high doses of theophylline may be associated with increased serum theophylline levels and possible theophylline toxicity. The dose of theophylline may require reduction while patients are receiving erythromycin.

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

Digoxin/Phenytoin: Concomitant administration of erythromycin and digoxin or phenytoin has been reported to result in elevated serum levels of these agents, leading to toxicity in some patients.

Oral Anticoagulants: There have been reports of increased prothrombin time when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to this drug may be more pronounced in the elderly (see PRECAUTIONS, Geriatrics).

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

Cyclosporin: A rise in plasma cyclosporin levels has been reported during concomitant administration of erythromycin.

Lincomycin/Clindamycin/Chloramphenicol: Erythromycin should be used with caution if administered concomitantly with lincomycin, clindamycin, or chloramphenicol. *In vitro* experiments have demonstrated that binding sites for erythromycin, lincomycin, clindamycin and chloramphenicol overlap and competitive inhibition may occur.

Triazolam/Midazolam: Erythromycin has been reported to decrease the clearance of triazolam and midazolam and thus may increase the pharmacologic effect of these drugs.

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.

Lovastatin: Patients receiving concomitant lovastatin and erythromycin should be carefully monitored; cases of rhabdomyolysis have been reported in seriously ill patients.

Cisapride/Pimozide: Rare cases of serious cardiovascular adverse events, including death, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed in patients taking cisapride concomitantly with macrolide antibiotics including erythromycin.

Atorvastatin: In healthy individuals, coadministration of erythromycin (500 mg QID) was associated with higher plasma concentrations of atorvastatin.

Quinidine: Drug interaction occurring with the concomitant administration of erythromycin and quinidine in their usual oral forms, resulting in QT prolongation, torsades de pointes and cardiac arrest has been reported. Caution and close monitoring is recommended when the drugs are administered concomitantly.

The use of erythromycin in patients taking concurrent drugs which are metabolized by cytochrome P450 (3A4) system may be associated with elevations in serum levels of these other drugs (e.g. pimozide, ergotamine, dihydroergotamine) (see CONTRAINDICATIONS). There have been reports of interactions of erythromycin with cyclosporine, tacrolimus, hexobarbital and phenytoin. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Pregnancy

The safety of erythromycin for use during pregnancy has not been established. Erythromycin crosses the placental barrier.

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.

Geriatrics:

Clinical studies with erythromycin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

There have been reports of prolonged QT syndrome in geriatric patients receiving erythromycin products.

Elderly patients may experience increased effects of oral anticoagulant therapy while undergoing treatment with erythromycin (see PRECAUTIONS, Drug Interactions.)

ADVERSE EFFECTS

Cardiovascular

QT prolongation, ventricular tachycardia, and torsades de pointes have been reported with macrolides, including erythromycin (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, Drug Interactions).

Gastrointestinal

Abdominal cramping and discomfort have been observed. Nausea, vomiting and diarrhea are also observed but less frequently. *Clostridium difficile*-associated disease has been observed (see WARNINGS).

Pancreatitis

There has been a report of a case of erythromycin-induced pancreatitis following erythromycin overdose.

Allergic Reactions

Urticaria, mild skin eruptions and anaphylaxis have been reported.

Hepatotoxicity

There have been reports of hepatic dysfunction, with or without jaundice, occurring in patients receiving erythromycin products.

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 loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

There have been isolated reports of transient central nervous system side effects including confusion, hallucinations, seizures and vertigo: however, a cause and effect relationship has not been established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

With oral doses of over 2 grams per day, abdominal discomfort, nausea or diarrhea may occur. There has been a report of a case of erythromycin-induced pancreatitis following erythromycin overdose. There is no specific treatment for accidental overdosage. Erythromycin should be discontinued and prompt elimination of unabsorbed drug and all other appropriate measures should be considered which may include use of activated charcoal; otherwise, treatment should be symptomatic. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

For management of suspected drug overdose, contact your Regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

Administration

Blood levels obtained upon administration of erythromycin (enteric-coated erythromycin pellets) in the presence of food are above minimum inhibitory concentrations (MIC's) of most organisms for which erythromycin is indicated. However, maximum blood levels are obtained in the fasting state (at least 30 minutes and preferably 2 hours before or after a meal).

Adults: The usual dose is 250 mg every 6 hours or 333 mg every 8 hours. If twice-a-day dosage is desired, the recommended dose is 500 mg every 12 hours. Dosage may be increased up to 4 g per day, depending on the severity of infection. Twice-a-day dosing is not recommended when doses larger than 1 g daily are administered.

Children: Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual dosage is 30-50 mg/kg/day in equally divided doses. For the treatment of more severe infections, this dosage may be doubled.

Dosage

Upper and Lower Respiratory Tract and Skin and Soft Tissue Infections: A therapeutic dosage of oral erythromycin should be administered for at least 10 days. The recommended dosage is 1 g per day given in divided doses (2, 3, or 4 times a day), depending on the erythromycin preparation chosen. Depending on the severity of infection, doses up to 4 g may be considered; however, a single dose should not exceed 1 g.

Pertussis: Although optimum dosage and duration of therapy 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.

Legionnaires' Disease: Large doses of up to 4 g daily in divided doses are necessary for the treatment of known or suspected Legionella infections.

Acne Vulgaris: Initially, up to 1 g per day is given 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.

Chlamydia Trachomatis Infections:

1. Conjunctivitis in infants:
Infants >2000 g: 30 mg/kg/day orally in divided doses for at least 14 days.
Infants >1 week to 1 month: 40 mg/kg/day orally in divided doses for at least 14 days.
Children 9 years or older as alternative treatment: 40 mg/kg/day orally in divided doses (max. 500 mg qid for 7 days or 250 mg qid for 14 days).
Note: Topical therapy alone for conjunctivitis is NOT adequate.
2. Urethral, endocervical or rectal infection in pregnant women and nursing mothers: 2 g/day orally in divided doses for 7 days.
3. Youth and adults: urethral endocervical, rectal infection: 2 g/day orally in divided doses for 7 days.

NOTE: Erythromycin dosages refer to the use of erythromycin base. Equivalent dosages of other formulations (EXCEPT the estolate which is contraindicated in pregnancy) may be substituted. If erythromycin has been used for treatment, repeat testing after completion of therapy is advisable.

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

Primary Syphilis: 2-4 g/day given in divided doses either 2, 3 or 4 times-a-day depending on the erythromycin preparation chosen, over a period of 10 to 15 days.

Prophylaxis: For continuous prophylaxis against recurrence of streptococcal infections in adults with a history of rheumatic heart disease, the recommended dose is 250 mg twice-a-day.

See PRECAUTIONS regarding Alfentanil.

Patient Instructions

Erythromycin capsules are not recommended for sprinkling, since the capsules are very full and some of the medication may be lost through spillage. If, however, the capsule is to be opened, care must be taken to open the capsule over food so as not to lose any of the pellets.

1. Hold the capsule with the clear end down. Gently twist off the orange cap to open.
2. Sprinkle the **ENTIRE** contents of the capsule on a spoonful of applesauce, fruit jellies, ice cream, etc. The pellets should not be chewed or crushed.
3. Have your child swallow the spoonful of applesauce, fruit jellies, or ice cream. Your child should drink some water to make sure all the pellets are swallowed.
4. If the pellets are accidentally spilled, start over with a new capsule.

AVAILABILITY OF DOSAGE FORMS

ERYTHRO-BASE

Each pink, oval, biconvex, film-coated tablet, identified “250”, contains erythromycin (base) 250 mg. Non-medicinal ingredients: microcrystalline cellulose, croscarmellose sodium, stearic acid, magnesium stearate, colloidal silicon dioxide, Hydroxypropyl methylcellose 2910 E5, polyethylene glycol 3350, titanium dioxide, carnuba wax and D &C Red #30 Aluminum Lake 30% Bottles of 100 and 1000 tablets.

ERYTHRO E-C

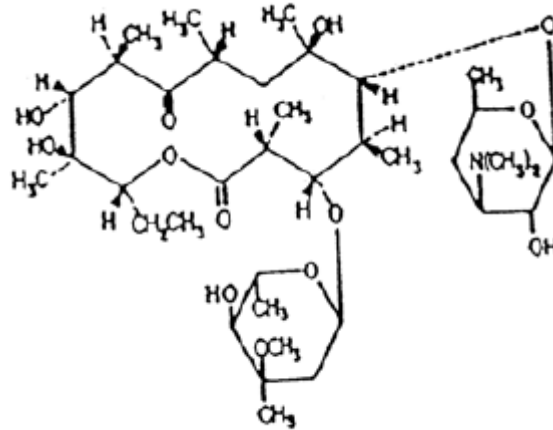
Each hard gelatin capsule with a white opaque body and an orange opaque cap with “250” imprinted on each capsule contains erythromycin (base) 250 mg. Non-medicinal ingredients: croscarmellose sodium, stearic acid, hydroxypropyl methylcellose 2910 E5, polyethylene glycol 8000, triethyl citrate, talc 600 mesh, methacrylic acid polymer type C. Capsule shell ingredients: titanium dioxide, gelatin and FD&C Yellow #6. Bottles of 100 capsules.

Each hard gelatin capsule with a white opaque body and a yellow opaque cap with “333” imprinted on each capsule contains erythromycin (base) 333 mg. Non-medicinal ingredients: croscarmellose sodium, stearic acid, hydroxypropyl methylcellose 2910 E5, polyethylene glycol 8000, triethyl citrate, talc 600 mesh, methacrylic acid polymer type C. Capsule shell ingredients: titanium dioxide, gelatin and FD&C Yellow #6. Bottles of 100 capsules.

Store at room temperature (15-30°C) in a tightly closed container.

PHARMACEUTICAL INFORMATION

Structural Formula:



Chemical Name:

(3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*,13S*,14R*)-4-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-L-ribo-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-b-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione.

Molecular Formula: $C_{37}H_{67}NO_{13}$

Molecular Weight: 733.94

MICROBIOLOGY

The in vitro activity of erythromycin against various microorganisms is shown in Table 1 below:

TABLE 1: In Vitro Spectrum of Erythromycin Activity

Organism	Typical Minimum Inhibitory Concentration (mcg/mL)			
	Mean	Range		
Gram-positive cocci:				
Staphylococcus aureus	0.4	0.005	-	>100
Streptococcus pyogenes	0.04	0.005	-	0.8
Streptococcus pneumoniae	0.05	0.006	-	0.2
Streptococcus viridans	0.06	0.02	-	0.1
Enterococcus	1.5	0.1	-	>400
Gram-positive bacilli:				
Clostridium perfringens	0.5	0.5	-	5
Corynebacterium diphtheriae	0.02	0.006	-	0.2
Listeria monocytogenes	0.16	0.1	-	0.3
Gram-negative cocci and bacilli:				
Neisseria gonorrhoeae	0.1	0.005	-	0.4
Neisseria meningitidis	0.4	0.1	-	0.8
Hemophilus influenzae	3.1	0.1	-	6
Bordetella pertussis	0.3	0.02	-	1.56
Bacteroides fragilis	1.5	0.12	-	>128
Brucella species	5	0.3	-	10
Legionella pneumophila	<0.5		-	
Others:				
Actinomyces israelii	0.5	0.2	-	0.5
Nocardia asteroides	25	0.2	-	>200
Mycoplasma pneumoniae	0.005	0.001	-	0.01
Mycobacterium kansasii	1	0.5	-	2

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 a 15 mg erythromycin disc and the dilution susceptibility test should be interpreted according to the criteria in Table 2:

TABLE 2

	Zone Diameter (mm)	Approximate MIC Correlate (mg/L)
Susceptible	>18	<2
Intermediate*	14 - 17	-
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 3.

Table 3

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

PHARMACOLOGY

The enteric coating of pellets in erythromycin capsules protects the erythromycin base from inactivation by gastric acidity. Because of their small size and enteric coating, the pellets may pass intact from the stomach to the small intestine and dissolve efficiently to allow absorption of erythromycin in a uniform manner.

Following oral administration, erythromycin base is readily absorbed from the upper part of the small intestine in the microbiologically active form. The drug is largely bound to plasma proteins,

and the freely dissociating bound fraction after administration of erythromycin base represents 90% of the total erythromycin absorbed. After absorption, erythromycin diffuses readily into most body fluids. In the absence of meningeal inflammation, low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin is excreted in breast milk. The drug crosses the placental barrier, but fetal plasma levels are low.

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. After oral administration, less than 5% of the administered dose can be recovered in the active form in the urine.

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

Bioavailability

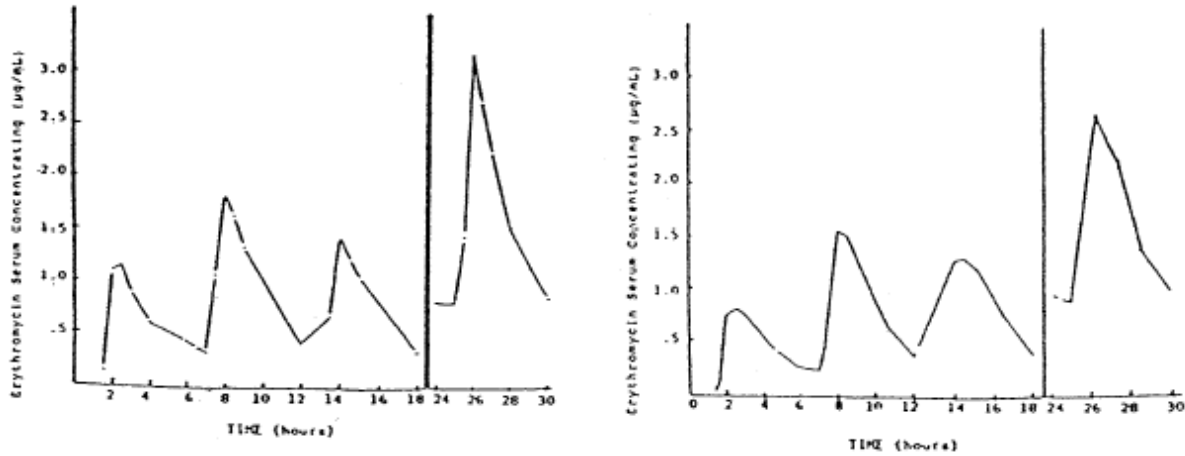
Effect of Fasting: Bioavailability studies of erythromycin capsules have been conducted in the fasting and non-fasting states. Single 250 mg doses were administered at 0, 6, 12, 18 and 24 hours. In one group (n=24), doses 1, 2, 3 and 5 were taken one hour before meals; the fourth dose was taken without food (Figure 1A). In a second group dosing similarly occurred five times at 6 hour intervals, but immediately before or after eating (Figure 1B). It was found that erythromycin capsules, when taken immediately before or after meals, demonstrate a decrease in bioavailability compared with the levels achieved when they are taken during fasting states.

Figure 1:

**Serum Concentrations of Erythromycin
Following Administration of Erythromycin Capsules, 250 mg**

1A: FASTING

1B: NON-FASTING



Effect of Dosage Form: Three comparative multiple-dose bioavailability studies were performed to evaluate the efficacy and reliability in absorption of erythromycin from erythromycin capsules versus enteric-coated tablets and film-coated stearate tablets. Five doses of 250 mg were given 6-hours apart and serum levels of erythromycin were analyzed in 24-26 volunteers in each study. erythromycin capsules gave a better and more reliable absorption than enteric-coated tablets and film-coated stearate tablets, whether the stearate was given 1 hour before food or immediately before a meal. Significant inter-individual variations in the absorption of erythromycin were observed and some patients did not achieve maximal serum levels.

Erythromycin 250: Erythromycin serum levels were determined in 27 subjects following oral administration of a single 250 mg or 500 mg dose of erythromycin 250 under fasting conditions. Mean pharmacokinetic parameters are reported in Table 4.

**TABLE 4: Mean (SD) Pharmacokinetic Parameters After
Administration of erythromycin 250 Capsules in the Fasting State**

<u>Parameter</u>	<u>Erythromycin 250 Treatment</u>	
	<u>1x250 mg Capsule</u>	<u>2x250 mg Capsules</u>
AUC ₀₋₁₆ (hr.mg/mL)	4.85 (1.71)	11.60 (4.43)
C _{max} (mg/mL)	1.39 (0.43)	2.73 (0.84)
T _{max} (hr)	3.67 (1.35)	4.00 (1.06)
K _{el} (hr ⁻¹)	0.403 (0.098)	0.389 (0.063)
t _{1/2} (hr)	1.81 (0.41)	1.83 (0.31)
0		

Erythromycin 333: A multidose study in 23 subjects receiving 1 capsule of erythromycin 333 every 8 hours (5 doses) or 1 capsule of erythromycin 250 every 6 hours (6 doses) produced average steady-state concentrations (0.89 vs. 0.92 mg/L) and normalized AUC's (10.69 vs. 11.06 mg.hr/L) which were not significantly different for the 2 dosing regimens.

TOXICOLOGY

The acute toxicity of erythromycin base (LD₅₀) is reported to be as follows in Table 5:

Table 5: Acute Toxicity of Erythromycin Base (LD₅₀)

Animal Species	Route of Administration	LD ₅₀ Value (mg/kg)
Mouse	P.O.	3112
	S.C.	>2500
Rat	P.O.	>3000
	S.C.	>2000
Guinea Pig	I.P.	413
Hamster	P.O.	3018

Chronic Toxicity

A chronic toxicity study with erythromycin base was performed in dogs and rats. Dogs were administered doses ranging up to 100 mg/kg/day for a period up to 90 weeks. Rats were given up to 4 g/kg/day for a period up to 85 weeks.

A review of the clinical signs and symptoms, weight curves, clinical laboratory values and gross and microscopic findings showed no drug-related toxicity in dogs or rats at the dose levels indicated.

Teratology Studies

There was no evidence of teratogenicity or other adverse effects on reproduction in female rats fed erythromycin base (up to 0.25% of diet) prior to and during mating, during gestation and through weaning of 2 successive litters.

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PART III: CONSUMER INFORMATION

PR ERYTHRO-BASE

Erythromycin (base) Tablets USP

PR ERYTHRO E-C

Erythromycin (base) Delayed-Release Capsules

This leaflet is part III of a three-part "Prescribing Information" published when erythromycin was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about erythromycin. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Erythromycin is an antibiotic for the treatment of the following mild to moderate infections by certain microorganisms, as determined by your doctor:

- upper and lower respiratory tract infections
- skin and other soft tissue infections including acne
- sexually transmitted diseases including syphilis and chlamydia

What it does:

Erythromycin belongs to the class of medicines called antibiotics. It works by killing or preventing growth of the bacteria responsible for your infection.

When it should not be used:

If you are allergic to erythromycin or any of the non-medicinal ingredients listed in this leaflet. (see **What the important non-medicinal ingredients are**)

If you are taking any of the following medication:
 - dihydroergotamine, ergotamine (for migraine)
 - cisapride* (for stomach disorders)
 - astemizole* and terfenadine* (antihistamines, for treating allergies)
 - pimozone (for psychiatric disorders)

* no longer marketed in Canada

What the medicinal ingredient is:

Erythromycin

What the important non-medicinal ingredients are:

ERYTHRO-BASE: microcrystalline cellulose, croscarmellose sodium, stearic acid, magnesium stearate, colloidal silicon dioxide, Hydroxypropyl methylcellulose 2910 E5, polyethylene glycol 3350, titanium dioxide, carnuba wax and D &C Red #30 Aluminum Lake 30%.

ERYTHRO E-C 250 mg: croscarmellose sodium, stearic acid, hydroxypropyl methylcellulose 2910 E5, polyethylene glycol 8000, triethyl citrate, talc 600 mesh, methacrylic acid polymer type C.

ERYTHRO E-C 333 mg: croscarmellose sodium, stearic acid, hydroxypropyl methylcellulose 2910 E5, polyethylene glycol 8000, triethyl citrate, talc 600 mesh, methacrylic acid polymer type C.

What dosage forms it comes in:

ERYTHRO-BASE 250 is a pink, oval, biconvex, film-coated tablet, identified "250", and contains erythromycin (base) 250 mg.

ERYTHRO E-C 250 is a hard gelatin capsule with a white opaque body and an orange opaque cap with "250" imprinted on each capsule contains erythromycin (base) 250 mg.

ERYTHRO E-C 333 is a hard gelatin capsule with a white opaque body and a yellow opaque cap with "333" imprinted on each capsule contains erythromycin (base) 333 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use erythromycin talk to your doctor or pharmacist if you:

- suffer from liver disease
- suffer from myasthenia gravis, a condition characterised by muscle weakness, difficulty chewing and swallowing and slurred speech
- Are pregnant or planning to become pregnant.
- Are breastfeeding or planning to breastfeed. Erythromycin is excreted in breast milk.

While taking erythromycin

- Follow your doctor's instructions carefully,
- Stop taking erythromycin immediately if you become pregnant and consult your doctor.
- Tell your doctor and pharmacist that you are taking erythromycin if you are about to start taking any new medicines.

- Do not stop taking your medicine until your doctor tells you to, even if you are feeling better.
- Do not use erythromycin to treat any other medical complaints unless your doctor tells you to.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with erythromycin include:

- alfentanil, midazolam and triazolam (sedatives which may be given before an operation)
- astemizole* and terfenadine* (antihistamines, for treating allergies)
- atorvastatin, lovastatin (for reducing blood cholesterol)
- carbamazepine, hexobarbital, phenytoin (for epilepsy)
- chloramphenicol, clindamycin and lincomycin (for infections)
- cyclosporin (for prevention of rejection after graft or organ transplant)
- cisapride* (for stomach disorders)
- digoxin and quinidine (for heart conditions)
- dihydroergotamine, ergotamine (for migraine)
- oral anticoagulants (for preventing blood clots)
- pimozone (for psychiatric disorders)
- theophylline (for breathing problems)

* no longer marketed in Canada

PROPER USE OF THIS MEDICATION

Usual dose:

Follow your doctor's instructions carefully about how much erythromycin to take and when to take it.

Erythromycin should be swallowed, at least 30 minutes and preferably 2 hours before or after a meal.

Antibacterial drugs including erythromycin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed.

Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by erythromycin or other antibacterial drugs in the future.

REMEMBER: This medication is for YOU. Never give it to others. It may harm them even if their symptoms are the same as yours.

Overdose:

Do not take more capsules than your doctor has told you to.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you should forget to take your capsule at the usual time, take it as soon as you remember unless it is time to take the next one. Continue with the remaining doses as before. Do not take more than one dose at a time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Erythromycin may cause side effects. If they occur, they are likely to be minor and temporary. However, some may be serious and need medical attention. Erythromycin may cause liver problems and liver dysfunction with symptoms such as nausea, vomiting, abdominal pain and discomfort, jaundice (yellowing of the skin and eyes), diarrhea, inflammation of the pancreas, itching and skin rashes, hearing problems (associated with very high doses), confusion, hallucinations, vertigo (dizziness, balance problem) and seizure.

Long-term use of erythromycin has been associated with the growth of not sensitive bacteria or fungi and bacteria initially sensitive to erythromycin. If such infections occur, stop taking erythromycin and call your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				REPORTING SUSPECTED SIDE EFFECTS
Symptoms/effect	Talk to your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist	<p>You can report any suspected adverse reactions associated with the use of health product to the Canada Vigilance Program by one of the following 3 ways:</p> <ul style="list-style-type: none"> • Report online at www.healthcanada.gc.ca/medeffect • Call toll-free to 1-866-234-2345 • Complete a Canada Vigilance Reporting Form and: <ul style="list-style-type: none"> ○ Fax toll-free to 1-866-678-6789, or ○ Mail to: Canada Vigilance Program Health Canada Postal Locator 0701E Ottawa, ON K1A 0K9 <p>Postage paid labels, Canada Vigilance Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.</p> <p>NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.</p>
	Only if severe	In all cases		
Diarrhea, watery diarrhea, bloody stools, with or without stomach cramps and fever (may indicate bowel inflammation or colitis)			√	
Hypersensitivity (allergic reaction) with symptoms such as swollen mouth, throat, lips, difficulty breathing, skin reactions (rash, blisters, hives.)			√	
Liver problems and liver dysfunction with symptoms such as nausea, vomiting, abdominal pain and discomfort, jaundice (yellowing of the skin and eyes)		√		
Irregularities of the heartbeat (palpitations)			√	

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc. at:

1-877-998-0997

This leaflet was prepared by AA Pharma Inc.

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This is not a complete list of side effects. For any unexpected effects while taking erythromycin, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature 15 to 30°C in a tightly closed container.