

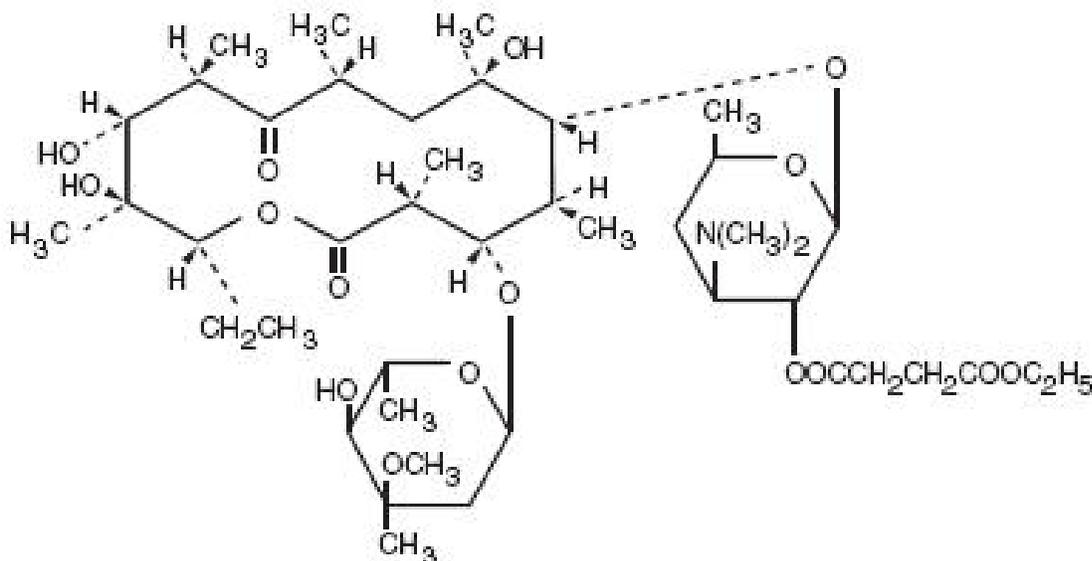
## ERY-PED®

(ERYTHROMYCIN ETHYLSUCCINATE, USP) Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ery-Ped and other antibacterial drugs, Ery-Ped should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### DESCRIPTION

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration. Erythromycin ethylsuccinate is known chemically as erythromycin 2'-(ethyl succinate). The molecular formula is  $C_{43}H_{75}NO_{16}$  and the molecular weight is 862.06. The structural formula is:



Ery-Ped 200 (erythromycin ethylsuccinate for oral suspension) when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 mL (teaspoonful) or 100 mg per 2.5 mL (dropperful) with an appealing fruit flavor. Ery-Ped 400 when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 mL (teaspoonful) with an appealing banana flavor.

These products are intended primarily for pediatric use but can also be used in adults.

### *Inactive Ingredients*

Ery-Ped 200, Ery-Ped 400:

Caramel, polysorbate, sodium citrate, sucrose, xanthan gum and artificial flavors.

## CLINICAL PHARMACOLOGY

Orally administered erythromycin ethylsuccinate suspension is readily and reliably absorbed under both fasting and nonfasting conditions.

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. 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 of erythromycin is excreted in active form in the urine.

Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk.

### *Microbiology:*

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis. Antagonism has been demonstrated *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Many strains of *Haemophilus influenzae* are resistant to erythromycin alone but are susceptible to erythromycin and sulfonamides used concomitantly.

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

Erythromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

### **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 Microorganisms:**

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

The following *in vitro* data are available.

Erythromycin exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 0.5 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and

effectiveness of erythromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Gram-positive Organisms:**

Viridans group streptococci

**Gram-negative Organisms:**

*Moraxella catarrhalis*

*Susceptibility Tests:*

**Dilution Techniques:**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1,2</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erythromycin powder. The MIC values should be interpreted according to the following criteria:

**For Staphylococcus spp**

<b><u>MIC (µg/mL)</u></b>	<b><u>Interpretation</u></b>
≤ 0.5	Susceptible (S)
1 – 4	Intermediate (I)
≥ 8	Resistant (R)

**For Streptococcus spp. and Streptococcus pneumoniae:**

<b><u>MIC (µg/mL)</u></b>	<b><u>Interpretation</u></b>
≤ 0.25	Susceptible (S)
0.5	Intermediate (I)
≥ 1	Resistant (R)

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.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard erythromycin powder should provide the following MIC values:

<b><u>Microorganism</u></b>	<b><u>MIC (µg/mL)</u></b>
<i>S. aureus</i> ATCC <sup>a</sup> 29213	0.25-1
<i>E. faecalis</i> ATCC 29212	1-4

*S. pneumoniae* ATCC 49619 0.03-0.12

<sup>a</sup> ATCC is a registered trademark of the American Type Culture Collection

### **Diffusion Techniques:**

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15- $\mu$ g erythromycin to test the susceptibility of microorganisms to erythromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15- $\mu$ g erythromycin disk should be interpreted according to the following criteria:

#### **For *Staphylococcus* spp:**

<b><u>Zone Diameter (mm)</u></b>	<b><u>Interpretation</u></b>
$\geq 23$	Susceptible (S)
14 – 22	Intermediate (I)
$\leq 13$	Resistant (R)

#### **For *Streptococcus* spp. and *Streptococcus pneumoniae*:**

<b><u>Zone Diameter (mm)</u></b>	<b><u>Interpretation</u></b>
$\geq 21$	Susceptible (S)
16 – 20	Intermediate (I)
$\leq 15$	Resistant (R)

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for erythromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15- $\mu$ g erythromycin disk should provide the following zone diameters in these laboratory test quality control strains:

<b><u>Microorganism</u></b>	<b><u>Zone Diameter (mm)</u></b>
<i>S. aureus</i> ATCC 25923	22-30
<i>S. pneumoniae</i> ATCC 49619	25-30

### **INDICATIONS AND USAGE**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ery-Ped and other antibacterial drugs, Ery-Ped should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Ery-Ped is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Haemophilus influenzae*

(when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower-respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes*.

Listeriosis caused by *Listeria monocytogenes*.

Pertussis (whooping cough) caused by *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.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

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

Erythrasma: In the treatment of infections due to *Corynebacterium minutissimum*.  
Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute Pelvic Inflammatory Disease Caused by *Neisseria gonorrhoeae*: 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. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Syphilis Caused by *Treponema pallidum*: Erythromycin is an alternate choice of treatment for primary syphilis in penicillin-allergic patients. In primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis*: Conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. 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*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Legionnaires' Disease caused by *Legionella pneumophila*. 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.

**Prophylaxis:**

***Prevention of Initial Attacks of Rheumatic Fever:***

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, e.g., tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.<sup>4</sup> The therapeutic dose should be administered for 10 days.

***Prevention of Recurrent Attacks of Rheumatic Fever:***

Penicillin or sulfonamides are considered by the American Heart Association 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 by the American Heart Association in the long-term prophylaxis of Streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).<sup>4</sup>

**CONTRAINDICATIONS**

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozide, or cisapride. (See **PRECAUTIONS** - Drug Interactions.)

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

**WARNINGS**

**Hepatotoxicity:**

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

**QT Prolongation:**

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

**Syphilis in Pregnancy:**

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration 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.

#### **Clostridium difficile Associated Diarrhea:**

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ery-Ped, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

#### **Drug Interactions**

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) (see **PRECAUTIONS – Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS – Drug Interactions**).

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. (See package insert for lovastatin).

#### **PRECAUTIONS**

**General:** Prescribing Ery-Ped in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS** sections.)

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

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 8-14 days and 10% for infants who took erythromycin for 15-21 days.<sup>5</sup> Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), 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.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

When indicated, incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy. Observational studies in humans have reported cardiovascular malformations after exposure to drug products containing erythromycin during early pregnancy.

**Information for Patients:** Patients should be counseled that antibacterial drugs including Ery-Ped should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Ery-Ped is prescribed to treat a bacterial infection, patients should be told that 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 Ery-Ped or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

### **Drug 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 that when oral erythromycin is given concurrently with theophylline there is a decrease in erythromycin serum concentrations of approximately 35%. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

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

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with various oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

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

*Ergotamine/dihydroergotamine:* 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. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

*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.

*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.

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

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozone, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed. (See **CONTRAINDICATIONS**.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin was co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See **CONTRAINDICATIONS**.)

*Colchicine:* Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

**Drug/Laboratory Test Interactions:** Erythromycin interferes with the fluorometric determination of urinary catecholamines.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term oral dietary studies conducted with erythromycin stearate in rats up to 400 mg/kg/day and in mice up to 500 mg/kg/day (approximately 1-2 fold of the maximum human dose on a body surface area basis) did not provide evidence of tumorigenicity. Erythromycin stearate did not show genotoxic potential in the Ames, and mouse lymphoma assays or induce chromosomal aberrations in CHO cells. 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 3 times the maximum human dose on a body surface area basis).

**Pregnancy: Teratogenic Effects. Pregnancy Category B:** There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body

surface area) prior to and during mating, during gestation, and through weaning. 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 and to pregnant rabbits at 125 mg/kg/day (approximately 1-3 times the maximum recommended human dose).

**Labor and Delivery:** The effect of erythromycin on labor and delivery is unknown.

**Nursing Mothers:** Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

**Pediatric Use:** See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.

**Geriatric Use:** Elderly patients, particularly those with reduced renal or hepatic function, may be at increased risk for developing erythromycin-induced hearing loss. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. (See **WARNINGS**).

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

Ery-Ped 200 contains 117.5 mg (5.1 mEq) of sodium per individual dose.

Ery-Ped 400 contains 117.5 mg (5.1 mEq) of sodium per individual dose.

Based on the 200 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 940 mg/day (40.8 mEq) of sodium. Based on the 400 mg/5 mL strength, at the usual recommended doses, adult patients would receive a total of 470 mg/day (20.4 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

## **ADVERSE REACTIONS**

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See **WARNINGS** section.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. (See **WARNINGS**.)

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

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

There have been rare reports of pancreatitis and convulsions.

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

### **OVERDOSAGE**

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures should be instituted.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

### **DOSAGE AND ADMINISTRATION**

Ery-Ped (erythromycin ethylsuccinate) oral suspensions 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 6 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 by administering one-third of the total daily dose every 8 hours.

The following dosage schedule is suggested for mild to moderate infections:

<b>Body Weight</b>	<b>Total Daily Dose</b>
Under 10 lbs	30-50 mg/kg/day 15-25 mg/lb/day
10 to 15 lbs	200 mg
16 to 25 lbs	400 mg
26 to 50 lbs	800 mg
51 to 100 lbs	1200 mg
over 100 lbs	1600 mg

**Adults:** 400 mg 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.

For adult dosage calculation, use a ratio of 400 mg of erythromycin activity as the ethylsuccinate to 250 mg of erythromycin activity as the stearate, base or estolate.

In the treatment of streptococcal infections, a therapeutic dosage of 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 treatment of urethritis due to *C. trachomatis* or *U. urealyticum*:** 800 mg three times a day for 7 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 amebiasis:** 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 Legionnaires' Disease:** Although optimal doses have not been established, doses utilized in reported clinical data were 1.6 to 4 g daily in divided doses.

## HOW SUPPLIED

Ery-Ped 200 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 100 mL (NDC 24338-132-13)

Ery-Ped 400 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 100 mL (NDC 24338-130-13)

## Recommended Storage:

Store Ery-Ped 200 and Ery-Ped 400, prior to mixing, below 86°F (30°C). After reconstitution, Ery-Ped 200 and Ery-Ped 400 must be stored at or below 77°F (25°C) and used within 35 days; refrigeration is not required.

## REFERENCES

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4. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*. 78(4):1082-1086, October 1988.
5. Honein, M.A., et. al.: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *The Lancet* 1999;354 (9196): 2101-5

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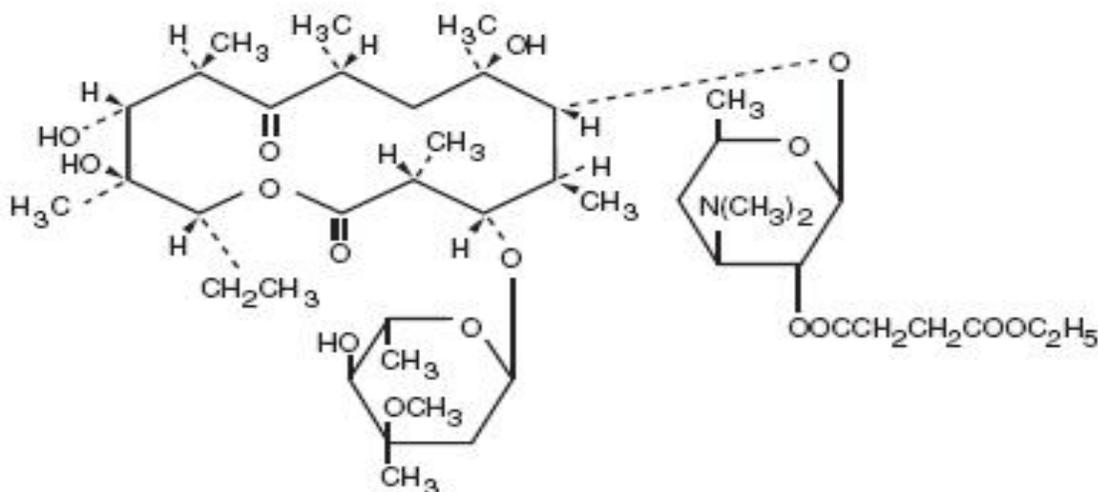
(Nos. 6302, 6305)

**E.E.S.<sup>®</sup>**  
**(ERYTHROMYCIN ETHYLSUCCINATE)**  
**R<sub>x</sub> only**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of E.E.S. and other antibacterial drugs, E.E.S. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**DESCRIPTION**

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration. Erythromycin ethylsuccinate is known chemically as erythromycin 2'-(ethylsuccinate). The molecular formula is C<sub>43</sub>H<sub>75</sub>NO<sub>16</sub> and the molecular weight is 862.06. The structural formula is:



E.E.S. Granules are intended for reconstitution with water. Each 5-mL teaspoonful of reconstituted cherry-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin.

The pleasant tasting, fruit-flavored liquids are supplied ready for oral administration.

E.E.S. 200 Liquid: Each 5-mL teaspoonful of fruit-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin.

E.E.S. 400 Liquid: Each 5-mL teaspoonful of orange-flavored suspension contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin.

Granules and ready-made suspensions are intended primarily for pediatric use but can also be used in adults.

E.E.S. 400 film-coated tablets: Each tablet contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin.

The film-coated tablets are intended primarily for adults or older children.

**Inactive Ingredients:**

E.E.S. Granules: Citric acid, FD&C Red No. 3, magnesium aluminum silicate, sodium carboxymethylcellulose, sodium citrate, sucrose and artificial flavor.

E.E.S. 400 film-coated tablets: Cellulosic polymers, confectioner's sugar (contains corn starch), corn starch, D&C Red No. 30, D&C Yellow No. 10, FD&C Red No. 40, magnesium stearate, polacrillin potassium, polyethylene glycol, propylene glycol, sodium citrate, sorbic acid, and titanium dioxide.

E.E.S. 200 Liquid: FD&C Red No. 40, methylparaben, polysorbate 60, propylparaben, sodium citrate, sucrose, water, xanthan gum and natural and artificial flavors.

E.E.S. 400 Liquid: D&C Yellow No. 10, FD&C Yellow No. 6, methylparaben, polysorbate 60, propylparaben, sodium citrate, sucrose, water, xanthan gum and natural and artificial flavors.

**CLINICAL PHARMACOLOGY**

Orally administered erythromycin ethylsuccinate suspensions and film-coated tablets are readily and reliably absorbed. Comparable serum 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 drug 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 of erythromycin is excreted in active form in the urine.

Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk.

**Microbiology**

Mechanism of Action

Erythromycin acts by inhibition of protein synthesis by binding 50S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

Resistance

The major route of resistance is modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity while efflux can also be significant.

Interactions With Other Antimicrobials

Antagonism exists in vitro between erythromycin and clindamycin, lincomycin, and chloramphenicol.

#### Antimicrobial Activity

Erythromycin has been shown to be active against most isolates of the following microorganisms both in vitro and in clinical infections [see *Indications and Usage (1)*].

##### Aerobic bacteria

###### Gram-positive bacteria:

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Listeria monocytogenes*

*Staphylococcus aureus* (resistant organisms may emerge during treatment)

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

###### Gram-negative bacteria:

*Bordetella pertussis*

*Haemophilus influenzae*

*Legionella pneumophila*

*Neisseria gonorrhoeae*

##### Other microorganisms:

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for erythromycin against isolates of similar genus or organism group. However, the efficacy of erythromycin in treating clinical infections caused by these bacteria has not been established in adequate and well controlled clinical trials.

##### Aerobic bacteria

###### Gram-positive bacteria:

*Viridans group streptococci*

###### Gram-negative bacteria:

*Moraxella catarrhalis*

#### Susceptibility Test Methods

When available the clinical microbiology laboratory should provide cumulative reports of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas

as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid in the selection of an appropriate antibacterial drug for treatment.

#### *Dilution Techniques*

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method<sup>1,2</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 1.

#### *Diffusion techniques*

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.<sup>2,3</sup> This procedure uses paper disks impregnated with 15 mcg erythromycin to test the susceptibility of microorganisms to erythromycin. The disc diffusion interpretive criteria are provided in Table 1.

**Table 1. Susceptibility Test Interpretive Criteria for Erythromycin**

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i>	≤ 0.5	1-4	≥ 8	≥ 23	14-22	≤ 13
<i>Streptococcus pneumoniae</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15
<i>Streptococcus pyogenes</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15

A report of *Susceptible (S)* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the site of infection.

A report of *Intermediate (I)* 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 a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation.

A report of *Resistant (R)* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

#### Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1,2,3</sup> Standard erythromycin powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 15 mcg disk, the criteria in Table 2 should be achieved.

**Table 2. Acceptable Quality Control Ranges for Erythromycin**

	<b>Minimum Inhibitory Concentrations (mcg/mL)</b>	<b>Disk Diffusion (zone diameters in mm)</b>
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	22-30
<i>Enterococcus faecalis</i> ATCC 29212	1-4	NA
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03-0.12	25-30

#### **INDICATIONS AND USAGE**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of E.E.S. and other antibacterial drugs, E.E.S. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

E.E.S. is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower-respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes*.

Listeriosis caused by *Listeria monocytogenes*.

Pertussis (whooping cough) caused by *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.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

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

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

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: 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. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

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

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. 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*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Legionnaires' Disease caused by *Legionella pneumophila*. 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.

### **Prophylaxis:**

#### *Prevention of Initial Attacks of Rheumatic Fever*

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, e.g., tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.<sup>4</sup>

The therapeutic dose should be administered for 10 days.

### *Prevention of Recurrent Attacks of Rheumatic Fever*

Penicillin or sulfonamides are considered by the American Heart Association 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 by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).<sup>4</sup>

## **CONTRAINDICATIONS**

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozone, or cisapride. (See **PRECAUTIONS - Drug Interactions.**)

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

## **WARNINGS**

### *Hepatotoxicity*

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

### *QT Prolongation*

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

### *Syphilis in Pregnancy*

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration 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.

### *Clostridium difficile Associated Diarrhea*

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including E.E.S., and may range in severity from mild diarrhea to fatal

colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

#### *Drug Interactions*

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) (see **PRECAUTIONS – Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS – Drug Interactions**).

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. (See package insert for lovastatin.)

## **PRECAUTIONS**

### **General**

Prescribing E.E.S. in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS** sections.)

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

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.<sup>5</sup>

Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), 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.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

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

### **Information for Patients**

Patients should be counseled that antibacterial drugs including E.E.S. should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When E.E.S. is prescribed to treat a bacterial infection, patients should be told that 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 E.E.S. or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

### **Drug 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 that when oral erythromycin is given concurrently with theophylline there is a decrease in erythromycin serum concentrations of approximately 35%. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

### *Verapamil*

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

### *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 oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with various oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

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

### *Ergotamine/dihydroergotamine*

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. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

### *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.

### *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.

### *Sildenafil (Viagra)*

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

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozone, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT<sub>c</sub> interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed. (See **CONTRAINDICATIONS**.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin is co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes, most likely due to inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See **CONTRAINDICATIONS**.)

#### *Colchicine*

Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

#### **Drug/Laboratory Test Interactions:**

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Long-term oral dietary studies conducted with erythromycin stearate in rats up to 400 mg/kg/day and in mice up to about 500 mg/kg/day (approximately 1 to 2 fold of the maximum human dose on a body surface area basis) did not provide evidence of tumorigenicity. Erythromycin stearate did not show genotoxic potential in the Ames, and mouse lymphoma assays or induce chromosomal aberrations in CHO cells. 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 3 times the maximum human dose on a body surface area basis).

#### **Pregnancy:**

##### *Teratogenic Effects*

### Pregnancy Category B:

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body surface area) prior to and during mating, during gestation, and through weaning.

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 and to pregnant rabbits at 125 mg/kg/day (approximately 1 to 3 times the maximum recommended human dose).

### **Labor and Delivery:**

The effect of erythromycin on labor and delivery is unknown.

### **Nursing Mothers:**

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

### **Pediatric Use:**

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.

### **Geriatric Use:**

Elderly patients, particularly those with reduced renal or hepatic function, may be at increased risk for developing erythromycin-induced hearing loss. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

Elderly patients may be more susceptible to the development of torsades de pointes arrhythmias than younger patients. (See **WARNINGS**.)

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

E.E.S.<sup>®</sup> Granules contains 25.9 mg (1.1 mEq) of sodium per individual dose.

The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

E.E.S. 400 film-coated contains 47 mg (2 mEq) of sodium per tablet and 10.0 mg (0.3 mEq) of potassium per tablet.

### **ADVERSE REACTIONS**

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See **WARNINGS** section.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS** section.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. (See **WARNINGS**.)

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

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

There have been rare reports of pancreatitis and convulsions.

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

### **OVERDOSAGE**

In case of overdose, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures should be instituted.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

### **DOSAGE AND ADMINISTRATION**

Erythromycin ethylsuccinate suspensions and film-coated 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 6 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 by administering one-third of the total daily dose every 8 hours.

The following dosage schedule is suggested for mild to moderate infections:

<b>Body Weight</b>	<b>Total Daily Dose</b>
Under 10 lbs	30 to 50 mg/kg/day 15 to 25 mg/lb/day
10 to 15 lbs	200 mg
16 to 25 lbs	400 mg
26 to 50 lbs	800 mg
51 to 100 lbs	1200 mg
over 100 lbs	1600 mg

#### *Adults*

400 mg 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.

For adult dosage calculation, use a ratio of 400 mg of erythromycin activity as the ethylsuccinate to 250 mg of erythromycin activity as the stearate, base or estolate.

In the treatment of streptococcal infections, a therapeutic dosage of 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 Treatment of Urethritis Due to *C. trachomatis* or *U. urealyticum***

800 mg three times a day for 7 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 Amebiasis**

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 Legionnaires' Disease**

Although optimal doses have not been established, doses utilized in reported clinical data were those recommended above (1.6 to 4 g daily in divided doses.)

**Directions for Mixing E.E.S. Granules**

*100 mL*

Add 77 mL water and shake vigorously. This makes 100 mL of suspension.

*200 mL*

Add 154 mL water and shake vigorously. This makes 200 mL of suspension.

**HOW SUPPLIED**

E.E.S. GRANULES 200 mg per 5 mL (erythromycin ethylsuccinate for oral suspension, USP) are pink granules with a cherry aroma and are supplied in 100-mL (NDC 24338-134-02) and 200-mL (NDC 24338-136-10) size bottles. Following reconstitution E.E.S. Granules become a pink opaque suspension with a cherry aroma.

E.E.S. 400 film-coated tablets (erythromycin ethylsuccinate tablets, USP) 400 mg, are supplied as pink oval tablets imprinted with the two letter designation, EE, in bottles of 100 (NDC 24338-100-13).

### **Recommended Storage**

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Store granules, prior to mixing, at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. After mixing, refrigerate and use within 10 days.

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6. Data on file, Arbor Pharmaceuticals, LLC.

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Arbor Pharmaceuticals, LLC  
Atlanta, GA 30328



(Nos. 5729, 6369)

## ERY-TAB®

(ERYTHROMYCIN DELAYED-RELEASE TABLETS, USP)

ENTERIC-COATED

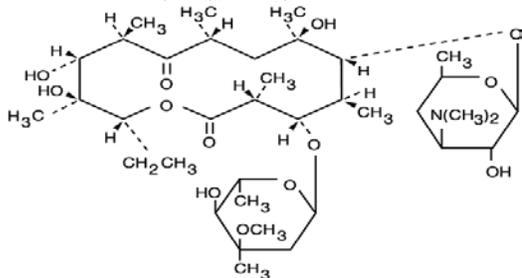
R<sub>x</sub> only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERY-TAB® and other antibacterial drugs, ERY-TAB® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### DESCRIPTION

ERY-TAB® (erythromycin delayed-release tablets) is an antibacterial product containing erythromycin base in a specially enteric-coated tablet. The coating protects the antibiotic from the inactivating effects of gastric acidity and permits efficient absorption of the antibiotic in the small intestine. ERY-TAB® tablets for oral administration are available in three dosage strengths, each white oval tablet containing 250 mg, 333 mg, or 500 mg of erythromycin as the free base. ERY-TAB® tablets comply with *USP Dissolution Test 1*.

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. Erythromycin is a white to off-white powder, slightly soluble in water, and soluble in alcohol, chloroform, and ether. Erythromycin is known chemically as (3R\*, 4S\*, 5S\*, 6R\*, 7R\*, 9R\*, 11R\*, 12R\*, 13S\*, 14R\*)-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl- $\alpha$ -L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione. The molecular formula is C<sub>37</sub>H<sub>67</sub>NO<sub>13</sub>, and the molecular weight is 733.94. The structural formula is:



### Inactive Ingredients

Ammonium hydroxide, colloidal silicon dioxide, croscarmellose sodium, crospovidone, diacetylated monoglycerides, hydroxypropyl cellulose, hypromellose, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sodium citrate, sorbitan monooleate, talc, and titanium dioxide.

### CLINICAL PHARMACOLOGY

Orally administered erythromycin base and its salts are readily absorbed in the microbiologically active form. Interindividual variations in the absorption of erythromycin are, however, observed, and some patients do not achieve optimal serum levels. Erythromycin is largely bound to plasma proteins. 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 the passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

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.

ERY-TAB<sup>®</sup> tablets are coated with a polymer whose dissolution is pH dependent. This coating allows for minimal release of erythromycin in acidic environments, e.g., stomach. The tablets are designed for optimal drug release and absorption in the small intestine. In multiple-dose, steady-state studies, ERY-TAB<sup>®</sup> tablets have demonstrated adequate drug delivery in both fasting and non-fasting conditions. Bioavailability data are available.

## **Microbiology**

### Mechanism of Action

Erythromycin acts by inhibition of protein synthesis by binding 50S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

### Mechanism of Resistance

The major route of resistance is modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity while efflux can also be significant.

### Interactions with Other Antibiotics

Antagonism exists *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Erythromycin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

### **Gram-positive Bacteria:**

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Listeria monocytogenes*

*Staphylococcus aureus* (resistant organisms may emerge during treatment)

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

### **Gram-negative Bacteria:**

*Bordetella pertussis*

*Haemophilus influenzae*

*Legionella pneumophila*

*Neisseria gonorrhoeae*

### **Other Microorganisms:**

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for erythromycin. However, the efficacy of erythromycin in treating clinical infections due to these bacteria has not been established in adequate and well controlled clinical trials.

### **Gram-positive Bacteria:**

*Viridans group streptococci*

### **Gram-negative Bacteria:**

*Moraxella catarrhalis*

### Susceptibility Test Methods

When available the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

#### Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method<sup>1,2</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in **Table 1**.

#### Diffusion techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.<sup>2,3</sup> This procedure uses paper disks impregnated with 15 mcg erythromycin to test the susceptibility of microorganisms to erythromycin. The disc diffusion interpretive criteria are provided in **Table 1**.

**Table 1. In Vitro Susceptibility Test Interpretive Criteria for Erythromycin**

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i>	≤ 0.5	1-4	≥ 8	≥ 23	14-22	≤ 13
<i>Streptococcus pneumoniae</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15
<i>Streptococcus pyogenes</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the site of infection necessary to inhibit growth of the pathogen. 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 product 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 antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

#### Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1,2,3,4</sup> Standard erythromycin powder should provide the following range of MIC values noted in **Table 2**. For the diffusion technique using the 15 mcg disk, the criteria in **Table 2** should be achieved.

**Table 2. Acceptable Quality Control Ranges for Erythromycin**

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1	NA

<i>Staphylococcus aureus</i> ATCC 25923	NA	22-30
<i>Enterococcus faecalis</i> ATCC 29212	1-4	NA
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03-0.12	25-30

## INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERY-TAB<sup>®</sup> and other antibacterial drugs, ERY-TAB<sup>®</sup> should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

ERY-TAB<sup>®</sup> tablets are indicated in the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Streptococcus pneumoniae*.

Listeriosis caused by *Listeria monocytogenes*.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Pertussis (whooping cough) caused by *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.

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

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

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythrocin<sup>™</sup> Lactobionate-I.V. (erythromycin lactobionate for injection, USP) followed by erythromycin base 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. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. 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*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Primary syphilis caused by *Treponema pallidum*. Erythromycin (oral forms only) is an alternative choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy.

Legionnaires' Disease caused by *Legionella pneumophila*. 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.

## **Prophylaxis**

### *Prevention of Initial Attacks of Rheumatic Fever*

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract e.g., tonsillitis, or pharyngitis).<sup>4</sup> Erythromycin is indicated for the treatment of penicillin-allergic patients. The therapeutic dose should be administered for ten days.

### *Prevention of Recurrent Attacks of Rheumatic Fever*

Penicillin or sulfonamides are considered by the American Heart Association 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 by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).<sup>4</sup>

## **CONTRAINDICATIONS**

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, cisapride, pimozide, ergotamine, or dihydroergotamine. (See **PRECAUTIONS – Drug Interactions.**)

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

## **WARNINGS**

### *Hepatotoxicity*

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

### *QT Prolongation*

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving

erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

#### *Syphilis in Pregnancy*

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration 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.

#### *Clostridium difficile Associated Diarrhea*

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ERY-TAB<sup>®</sup>, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

#### *Drug Interactions*

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) (see **PRECAUTIONS – Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS – Drug Interactions**).

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. (See package insert for lovastatin.)

## **PRECAUTIONS**

### ***General***

Prescribing ERY-TAB<sup>®</sup> in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS**.)

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

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 8-14 days and 10% for infants who took erythromycin for 15-21 days.<sup>5</sup> Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal Chlamydia trachomatis infections), 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.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

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

Observational studies in humans have reported cardiovascular malformations after exposure to drug products containing erythromycin during early pregnancy.

### ***Information for Patients***

Patients should be counseled that antibacterial drugs including ERY-TAB<sup>®</sup> should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ERY-TAB<sup>®</sup> is prescribed to treat a bacterial infection, patients should be told that 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 ERY-TAB<sup>®</sup> or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

### ***Drug 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 that when oral erythromycin is given concurrently with theophylline there is a decrease in erythromycin serum concentrations of approximately 35%. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

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

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

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

#### *Ergotamine/dihydroergotamine*

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. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

#### *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.

#### *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.

#### *Sildenafil (Viagra)*

Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered. (See Viagra package insert.) There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methyl-prednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT<sub>c</sub> interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed. (See **CONTRAINDICATIONS**.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin was co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and

torsades de pointes, most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See **CONTRAINDICATIONS**.)

### *Colchicine*

Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

### ***Drug/Laboratory Test Interactions***

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

### ***Carcinogenesis, Mutagenesis, Impairment of Fertility***

Long-term oral dietary studies conducted with erythromycin stearate in rats up to 400 mg/kg/day and in mice up to about 500 mg/kg/day (approximately 1-2 fold of the maximum human dose on a body surface area basis) did not provide evidence of tumorigenicity. Erythromycin stearate did not show genotoxic potential in the Ames, and mouse lymphoma assays or induce chromosomal aberrations in CHO cells. 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 3 times the maximum human dose on a body surface area basis).

### ***Pregnancy***

#### *Teratogenic Effects*

#### Pregnancy Category B

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body surface area) prior to and during mating, during gestation, and through weaning. 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 and to pregnant rabbits at 125 mg/kg/day (approximately 1-3 times the maximum recommended human dose).

### ***Labor and Delivery***

The effect of erythromycin on labor and delivery is unknown.

### ***Nursing Mothers***

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

### ***Pediatric Use***

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.

### ***Geriatric Use***

Elderly patients, particularly those with reduced renal or hepatic function, may be at increased risk for developing erythromycin-induced hearing loss. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. (See **WARNINGS**).

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

Ery-Tab<sup>®</sup> Delayed Release Tablets (250 mg) contain 8.3 mg (0.4 mEq) of sodium per tablet.  
Ery-Tab<sup>®</sup> Delayed Release Tablets (333 mg) contain 11.2 mg (0.5 mEq) of sodium per tablet.  
Ery-Tab<sup>®</sup> Delayed Release Tablets (500 mg) contain 16.7 mg (0.7 mEq) of sodium per tablet.

The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

### **ADVERSE REACTIONS**

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See **WARNINGS**.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. (See **WARNINGS**.)

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

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

There have been rare reports of pancreatitis and convulsions.

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

### **OVERDOSAGE**

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures should be instituted.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

### **DOSAGE AND ADMINISTRATION**

In most patients, ERY-TAB<sup>®</sup> (erythromycin delayed-release tablets) are well absorbed and may be dosed orally without regard to meals. However, optimal blood levels are obtained when ERY-TAB<sup>®</sup> 250 mg, ERY-TAB<sup>®</sup> 333 mg or ERY-TAB<sup>®</sup> 500 mg tablets are given in the fasting state (at least ½ hour and preferably 2 hours before meals).

#### *Adults*

The usual dose is 250 mg four times daily in equally spaced doses. The 333 mg tablet is recommended if dosage is desired 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 according to the severity of the infection. However, 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 to 50 mg/kg/day, in equally divided doses. For more severe infections, this dose may be doubled but should not exceed 4 g per day.

In the treatment of streptococcal infections of the upper respiratory tract (e.g., tonsillitis or pharyngitis), the therapeutic dosage of erythromycin should be administered for at least ten days.

The American Heart Association suggests a dosage of 250 mg of erythromycin orally, twice a day in long-term prophylaxis of streptococcal upper respiratory tract infections for the prevention of recurring attacks of rheumatic fever in patients allergic to penicillin and sulfonamides.<sup>4</sup>

#### **Conjunctivitis of the Newborn Caused by *Chlamydia trachomatis***

Oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 2 weeks.<sup>4</sup>

#### **Pneumonia of Infancy Caused by *Chlamydia trachomatis***

Although the optimal duration of therapy has not been established, the recommended therapy is oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 3 weeks.

#### **Urogenital Infections During Pregnancy Due to *Chlamydia trachomatis***

Although the optimal dose and duration of therapy have not been established, the suggested treatment is 500 mg of erythromycin by mouth four times a day or two erythromycin 333 mg tablets orally every 8 hours on an empty stomach for at least 7 days. For women who cannot tolerate this regimen, a decreased dose of one erythromycin 500 mg tablet orally every 12 hours, one 333 mg tablet orally every 8 hours or 250 mg by mouth four times a day should be used for at least 14 days.<sup>6</sup>

#### **For adults with uncomplicated urethral, endocervical, or rectal infections caused by *Chlamydia trachomatis*, when tetracycline is contraindicated or not tolerated**

500 mg of erythromycin by mouth four times a day or two 333 mg tablets orally every 8 hours for at least 7 days.<sup>6</sup>

#### **For patients with nongonococcal urethritis caused by *Ureaplasma urealyticum* when tetracycline is contraindicated or not tolerated**

500 mg of erythromycin by mouth four times a day or two 333 mg tablets orally every 8 hours for at least seven days.<sup>6</sup>

#### **Primary Syphilis**

30 to 40 g given in divided doses over a period of 10 to 15 days.

#### **Acute Pelvic Inflammatory Disease Caused by *N. Gonorrhoeae***

500 mg Erythrocin Lactobionate-I.V. (erythromycin lactobionate for injection, USP) every 6 hours for 3 days, followed by 500 mg of erythromycin base orally every 12 hours, or 333 mg of erythromycin base orally every 8 hours for 7 days.

#### **Intestinal Amebiasis**

##### *Adults*

500 mg every 12 hours, 333 mg every 8 hours or 250 mg every 6 hours for 10 to 14 days.

##### *Children*

30 to 50 mg/kg/day in divided doses for 10 to 14 days.

#### **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.

#### **Legionnaires' Disease**

Although optimal dosage has not been established, doses utilized in reported clinical data were 1 to 4 g daily in divided doses.

#### Preoperative Prophylaxis for Elective Colorectal Surgery:

Listed below is an example of a recommended bowel preparation regimen.

A proposed surgery time of 8:00 a.m. has been used.

Pre-op Day 3: Minimum residue or clear liquid diet. Bisacodyl, 1 tablet orally at 6:00 p.m.

Pre-op Day 2: Minimum residue or clear liquid diet. Magnesium sulfate, 30 mL, 50% solution (15 g) orally at 10:00 a.m., 2:00 p.m. and 6:00 p.m. Enema at 7:00 p.m. and 8:00 p.m.

Pre-op Day 1: Clear liquid diet. Supplemental (IV) fluids as needed. Magnesium sulfate, 30 mL, 50% solution (15 g) orally at 10:00 a.m. and 2:00 p.m. Neomycin sulfate (1.0 g) and erythromycin base (two 500 mg tablets, three 333 mg tablets or four 250 mg tablets) orally at 1:00 p.m., 2:00 p.m. and 11:00 p.m. No enema.

Day of Operation: Patient evacuates rectum at 6:30 a.m. for scheduled operation at 8:00 a.m.

#### HOW SUPPLIED

ERY-TAB<sup>®</sup> (erythromycin delayed-release tablets, USP) are supplied as white oval enteric-coated tablets debossed on one side with the Arbor logo, A, and on the other side with a two letter Code designation, EC for the 250 mg tablets, EH for the 333 mg tablets, and ED for the 500 mg tablets, in the following package sizes:

250 mg tablets: bottles of 30 (NDC 24338-122-03)

250 mg tablets: bottles of 100 (NDC 24338-122-13)

333 mg tablets: bottles of 30 (NDC 24338-124-03)

333 mg tablets: bottles of 100 (NDC 24338-124-13)

500 mg tablets: bottles of 30 (NDC 24338-126-03)

500 mg tablets: bottles of 100 (NDC 24338-126-13)

#### Recommended Storage

Store below 86°F (30°C).

#### REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard – Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-third Informational Supplement*. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition* CLSI document M02-A11. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

4. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*. 78(4):1082-1086, October 1988.
5. Honein, M.A., et al.: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *The Lancet* 1999;354 (9196): 2101-5.
6. Data on file, Arbor Pharmaceuticals, LLC.

ETAB-PI-02

Revised: August 2018

Arbor Pharmaceuticals, LLC

Atlanta, GA 30328 USA



List 6304, 6320, 6321

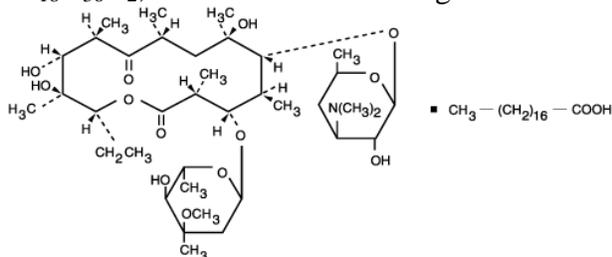
**ERYTHROCIN<sup>®</sup> STEARATE**  
**ERYTHROMYCIN STEARATE**  
**TABLETS, USP**  
**Film-coated Tablets**  
**Rx only**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets and other antibacterial drugs, ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**DESCRIPTION**

ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets (erythromycin stearate tablets, USP) are an antibacterial product containing the stearate salt of erythromycin in a unique film coating.

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. Erythromycin is a white to off-white powder, slightly soluble in water, and soluble in alcohol, chloroform, and ether. Erythromycin stearate is known chemically as erythromycin octadecanoate. The molecular formula of erythromycin stearate is C<sub>37</sub>H<sub>67</sub>NO<sub>13</sub> • C<sub>18</sub>H<sub>36</sub>O<sub>2</sub>, and the molecular weight is 1018.43. The structural formula is:



**Inactive Ingredients:**

250 mg tablet: Cellulosic polymers, corn starch, D&C Red No. 7, polyacrilin potassium, polyethylene glycol, povidone, propylene glycol, sodium carboxymethylcellulose, sodium citrate, sorbic acid, sorbitan monooleate and titanium dioxide.

**CLINICAL PHARMACOLOGY**

Orally administered erythromycin base and its salts are readily absorbed in the microbiologically active form. Interindividual variations in the absorption of erythromycin are, however, observed, and some patients do not achieve optimal serum levels. Erythromycin is largely bound to plasma proteins. 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 the passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

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.

Orally administered ERYTHROCIN<sup>®</sup> STEARATE tablets are readily and reliably absorbed. Optimal serum levels of erythromycin are reached when the drug is taken in the fasting state or immediately before meals.

## **Microbiology**

### Mechanism of Action

Erythromycin acts by inhibition of protein synthesis by binding 50S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

### Mechanism of Resistance

The major route of resistance is modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity while efflux can also be significant.

### Interactions with Other Antibiotics

Antagonism exists *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Erythromycin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

### **Gram-positive Bacteria:**

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Listeria monocytogenes*

*Staphylococcus aureus* (resistant organisms may emerge during treatment)

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

### **Gram-negative Bacteria:**

*Bordetella pertussis*

*Haemophilus influenzae*

*Legionella pneumophila*

*Neisseria gonorrhoeae*

### **Other Microorganisms:**

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for erythromycin. However, the efficacy of erythromycin in treating clinical infections due to these bacteria has not been established in adequate and well controlled clinical trials.

**Gram-positive Bacteria:**

*Viridans group streptococci*

**Gram-negative Bacteria:**

*Moraxella catarrhalis*

*Susceptibility Test Methods*

When available the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method<sup>1,2</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in **Table 1**.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.<sup>2,3</sup> This procedure uses paper disks impregnated with 15 mcg erythromycin to test the susceptibility of microorganisms to erythromycin. The disc diffusion interpretive criteria are provided in **Table 1**.

**Table 1. *In Vitro* Susceptibility Test Interpretive Criteria for Erythromycin**

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i>	≤ 0.5	1-4	≥ 8	≥ 23	14-22	≤ 13
<i>Streptococcus pneumoniae</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15
<i>Streptococcus pyogenes</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15

A report of “Susceptible” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the site of infection necessary to inhibit growth of the pathogen. 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 product 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 antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

**Quality Control:**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1, 2, 3, 4</sup> Standard erythromycin powder should provide the following range of MIC values noted in **Table 2**. For the diffusion technique using the 15 mcg disk, the criteria in **Table 2** should be achieved.

**Table 2. Acceptable Quality Control Ranges for Erythromycin**

<b>QC Strain</b>	<b>Minimum Inhibitory Concentrations (mcg/mL)</b>	<b>Disk Diffusion (zone diameters in mm)</b>
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	22-30
<i>Enterococcus faecalis</i> ATCC 29212	1-4	NA
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03-0.12	25-30

**INDICATIONS AND USAGE**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets and other antibacterial drugs, ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

ERYTHROCIN<sup>®</sup> STEARATE tablets are indicated in the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Streptococcus pneumoniae*.

Listeriosis caused by *Listeria monocytogenes*.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Pertussis (whooping cough) caused by *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.

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

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

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythrocin™ Lactobionate- I.V. (erythromycin lactobionate for injection, USP) followed by erythromycin base 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. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. 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*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Primary syphilis caused by *Treponema pallidum*. Erythromycin (oral forms only) is an alternative choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy.

Legionnaires' Disease caused by *Legionella pneumophila*. 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.

## **Prophylaxis**

### *Prevention of Initial Attacks of Rheumatic Fever*

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract e.g., tonsillitis, or pharyngitis).<sup>4</sup> Erythromycin is indicated for the treatment of penicillin-allergic patients. The therapeutic dose should be administered for ten days.

### *Prevention of Recurrent Attacks of Rheumatic Fever*

Penicillin or sulfonamides are considered by the American Heart Association 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 by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).<sup>4</sup>

## **CONTRAINDICATIONS**

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, cisapride, pimozide, ergotamine, or dihydroergotamine. (See **PRECAUTIONS - Drug Interactions.**)

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

## **WARNINGS**

### *Hepatotoxicity*

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

### *QT Prolongation*

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

### *Syphilis in Pregnancy*

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration 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.

### *Clostridium difficile Associated Diarrhea*

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### *Drug Interactions*

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) (see **PRECAUTIONS-Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS- Drug Interactions**).

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. (See package insert for lovastatin.)

## **PRECAUTIONS**

### ***General***

Prescribing ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS**.)

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

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.<sup>5</sup> Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal Chlamydia trachomatis infections), 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.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

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

Observational studies in humans have reported cardiovascular malformations after exposure to drug products containing erythromycin during early pregnancy.

### ***Information for Patients***

Patients should be counseled that antibacterial drugs including ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets are prescribed to treat a bacterial infection, patients should be told that 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 ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

## ***Drug 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 that when oral erythromycin is given concurrently with theophylline there is a decrease in erythromycin serum concentrations of approximately 35%. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

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

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

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

### ***Ergotamine/dihydroergotamine***

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. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

### ***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.

#### *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.

#### *Sildenafil (Viagra)*

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

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methyl-prednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozone, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT<sub>c</sub> interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed. (See **CONTRAINDICATIONS**.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin was co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes, most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See **CONTRAINDICATIONS**).

#### *Colchicine*

Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

### ***Drug/Laboratory Test interactions***

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

### ***Carcinogenesis, Mutagenesis, Impairment of Fertility***

Long-term oral dietary studies conducted with erythromycin stearate in rats up to 400 mg/kg/day and in mice up to about 500 mg/kg/day (approximately 1 to 2 fold of the maximum human dose on a body surface area basis) did not provide evidence of tumorigenicity. Erythromycin stearate did not show genotoxic potential in the Ames, and mouse lymphoma assays or induce chromosomal aberration in CHO cells. 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 3 times the maximum human dose on a body surface area basis).

### **Pregnancy**

#### ***Teratogenic Effects***

#### **Pregnancy Category B**

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body surface area) prior to and during mating, during gestation, and through weaning. 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 and to pregnant rabbits at 125 mg/kg/day (approximately 1 to 3 times the maximum recommended human dose).

#### ***Labor and Delivery***

The effect of erythromycin on labor and delivery is unknown.

#### ***Nursing Mothers***

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

#### ***Pediatric Use***

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.

#### ***Geriatric Use***

Elderly patients, particularly those with reduced renal or hepatic function, may be at increased risk for developing erythromycin-induced hearing loss. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Elderly patients may be more susceptible to the development of torsades de pointes arrhythmias than younger patients. (See **WARNINGS**).

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

Erythrocin Stearate Film-coated tablets (250 mg) contain 56.7 mg (2.5 mEq) of sodium and 5.0 mg (0.1 mEq) of potassium per tablet.

The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

### **ADVERSE REACTIONS**

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See **WARNINGS**.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. (See **WARNINGS**.)

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

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

There have been rare reports of pancreatitis and convulsions.

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

### **OVERDOSAGE**

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures should be instituted.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

### **DOSAGE AND ADMINISTRATION**

In most patients, ERYTHROCIN<sup>®</sup> STEARATE Film-coated tablets are well absorbed and may be dosed orally without regard to meals. However, optimal blood levels are obtained when ERYTHROCIN<sup>®</sup> STEARATE tablets are given in the fasting state (at least ½ hour and preferably 2 hours before meals).

#### *Adults*

The usual dosage is 250 mg every 6 hours; or 500 mg every 12 hours. Dosage may be increased up to 4 g per day according to the severity of the infection. However, 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 to 50 mg/kg/day, in equally divided doses. For more severe infections this dosage may be doubled but should not exceed 4 g per day.

In the treatment of streptococcal infections of the upper respiratory tract (e.g., tonsillitis or pharyngitis), the therapeutic dosage of erythromycin should be administered for at least ten days.

The American Heart Association suggests a dosage of 250 mg of erythromycin orally, twice a day in long-term prophylaxis of streptococcal upper respiratory tract infections for the prevention of recurring attacks of rheumatic fever in patients allergic to penicillin and sulfonamides.<sup>4</sup>

### **Conjunctivitis of the Newborn Caused by *Chlamydia trachomatis***

Oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 2 weeks.<sup>4</sup>

### **Pneumonia of Infancy Caused by *Chlamydia trachomatis***

Although the optimal duration of therapy has not been established, the recommended therapy is oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 3 weeks.

### **Urogenital Infections During Pregnancy Due to *Chlamydia trachomatis***

Although the optimal dose and duration of therapy have not been established, the suggested treatment is 500 mg of erythromycin by mouth four times a day or two erythromycin 333 mg tablets orally every 8 hours on an empty stomach for at least 7 days. For women who cannot tolerate this regimen, a decreased dose of one erythromycin 500 mg tablet orally every 12 hours, one 333 mg tablet orally every 8 hours or 250 mg by mouth four times a day should be used for at least 14 days.<sup>6</sup>

### **For adults with uncomplicated urethral, endocervical, or rectal infections caused by *Chlamydia trachomatis*, when tetracycline is contraindicated or not tolerated**

500 mg of erythromycin by mouth four times a day or two 333 mg tablets orally every 8 hours for at least 7 days.<sup>6</sup>

### **For patients with nongonococcal urethritis caused by *Ureaplasma urealyticum* when tetracycline is contraindicated or not tolerated**

500 mg of erythromycin by mouth four times a day or two 333 mg tablets orally every 8 hours for at least seven days.<sup>6</sup>

### **Primary Syphilis**

30 to 40 g given in divided doses over a period of 10 to 15 days.

### **Acute Pelvic Inflammatory Disease Caused by *N. gonorrhoeae***

500 mg Erythrocin Lactobionate-I.V. (erythromycin lactobionate for injection, USP) every 6 hours for 3 days, followed by 500 mg of erythromycin base orally every 12 hours, or 333 mg of erythromycin base orally every 8 hours for 7 days.

### **Intestinal Amebiasis**

### *Adults*

500 mg every 12 hours, 333 mg every 8 hours or 250 mg every 6 hours for 10 to 14 days.

### *Children*

30 to 50 mg/kg/day in divided doses for 10 to 14 days.

### **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.

### **Legionnaires' Disease**

Although optimal dosage has not been established, doses utilized in reported clinical data were 1 to 4 g daily in divided doses.

### **HOW SUPPLIED**

ERYTHROCIN<sup>®</sup> STEARATE Film-coated Tablets (erythromycin stearate tablets, USP) are supplied in the following strengths and packages.

ERYTHROCIN<sup>®</sup> STEARATE Film-coated, 250 mg pink tablets imprinted with the Product Code designation ES:

Bottles of 30.....(NDC 24338-106-03)

Bottles of 100.....(NDC 24338-106-20)

### **Recommended Storage**

Store below 86°F (30°C).

### **REFERENCES**

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard – Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-third Informational Supplement*. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition*. CLSI document M02-A11. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
4. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*. 78(4):1082-1086, October 1988.
5. Honein, M.A., et al.: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *The Lancet* 1999;354 (9196): 2101-5.

6. Data on file, Arbor Pharmaceuticals, LLC.

EST-PI-02

Revised: August 2018

Arbor Pharmaceuticals, LLC  
Atlanta, GA 30328 USA



(Nos. 6346)

# ERYTHROMYCIN DELAYED-RELEASE CAPSULES, USP

R<sub>x</sub> only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Erythromycin Delayed-release Capsules, USP and other antibacterial drugs, Erythromycin Delayed-release Capsules, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

## DESCRIPTION

Erythromycin Delayed-release Capsules, USP contain enteric-coated pellets of erythromycin base for oral administration.

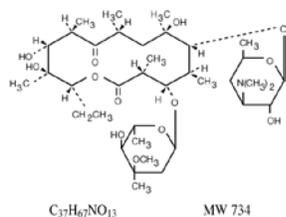
Each Erythromycin Delayed-release Capsule, USP contains 250 mg of erythromycin base.

## Inactive Ingredients

Cellulosic polymers, citrate ester, D&C Red No. 30, D&C Yellow No. 10, magnesium stearate and povidone. The capsule shell contains FD&C Blue No. 1, FD&C Red No. 3, gelatin, and titanium dioxide.

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids but it is the base which is microbiologically active. Erythromycin base is (3R\*, 4S\*, 5S\*, 6R\*, 7R\*, 9R\*, 11R\*, 12R\*, 13S\*, 14R\*)-4-[(2,6-Dideoxy-3-C-methyl-3-O-methyl- $\alpha$ -L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xyllo-hexopyranosyl]oxy]-oxacyclo-tetradecane-2,10-dione.

## ERYTHROMYCIN



## CLINICAL PHARMACOLOGY

Orally administered erythromycin base and its salts are readily absorbed in the microbiologically active form. Interindividual variations in the absorption of erythromycin are, however, observed, and some patients do not achieve acceptable serum levels. Erythromycin is largely bound to plasma proteins, and the freely dissociating bound fraction after administration of erythromycin base represents 90 percent 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 the passage of the drug across the blood-brain barrier increases in meningitis. The drug is excreted in human milk. The drug crosses the placental barrier, but fetal plasma levels are low. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

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 percent of the administered dose can be recovered in the active form in the urine.

The enteric coating of pellets in Erythromycin Delayed-release Capsules, USP protects the erythromycin base from inactivation by gastric acidity. Because of their small size and enteric coating, the pellets readily pass intact from the stomach to the small intestine and dissolve efficiently to allow absorption of erythromycin in a uniform manner. After administration of a single dose of a 250 mg Erythromycin Delayed-release Capsule, USP peak serum levels in the range of 1.13 to 1.68 mcg/mL are attained in approximately 3 hours and decline to 0.30 to 0.42 mcg/mL in 6 hours. Optimal conditions for stability in the presence of gastric secretion and for complete absorption are attained when erythromycin is taken on an empty stomach.

### **Microbiology:**

#### Mechanism of Action

Erythromycin acts by inhibition of protein synthesis by binding 50 S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

#### Mechanism of Resistance

The major route of resistance is modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity, while efflux can also be significant.

#### Interaction with other Antimicrobials

Antagonism exists *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Erythromycin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Gram-positive bacteria:

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Listeria monocytogenes*

*Staphylococcus aureus*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

Gram-negative bacteria:

*Bordetella pertussis*

*Haemophilus influenzae*

*Legionella pneumophila*

*Neisseria gonorrhoeae*

Other Microorganisms:

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

### Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

#### Dilution techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method<sup>1,2</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 1.

#### Diffusion techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.<sup>2,3</sup> This procedure uses paper disks impregnated with 15 mcg erythromycin to test the susceptibility of microorganisms to erythromycin. The disc diffusion interpretive criteria are provided in **Table 1**.

**Table 1. *In vitro* Susceptibility Test Interpretive Criteria for Erythromycin**

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i>	≤ 0.5	1-4	≥ 8	≥ 23	14-22	≤ 13
<i>Streptococcus pneumoniae</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15

*Streptococcus pyogenes*      ≤ 0.25      0.5      ≥ 1      ≥ 21      16-20      ≤ 15

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the site of infection necessary to inhibit growth of the pathogen. 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 a 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 antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

### Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1,2,3,4</sup> Standard erythromycin powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the erythromycin 15 mcg disk the criteria in Table 2 should be achieved.

**Table 2. Acceptable Quality Control Ranges for Erythromycin**

<b>QC Strain</b>	<b>Minimum Inhibitory Concentrations (mcg/mL)</b>	<b>Disk Diffusion (zone diameters in mm)</b>
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	22-30
<i>Enterococcus faecalis</i> ATCC 29212	1-4	NA
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03-0.12	25-30

### INDICATIONS AND USAGE

Erythromycin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved) (see appropriate sulfonamide labeling for prescribing information).

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes*.

Listeriosis caused by *Listeria monocytogenes*.

Pertussis (whooping cough) caused by *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.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

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

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

Syphilis caused by *Treponema pallidum*: Erythromycin is an alternate choice of treatment for primary syphilis in penicillin-allergic patients. In primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythromycin lactobionate for injection, USP followed by erythromycin base 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. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. 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*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Legionnaires' Disease caused by *Legionella pneumophila*. 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.

**Prophylaxis:***Prevention of Initial Attacks of Rheumatic Fever:*

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, e.g., tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.<sup>4</sup> The therapeutic dose should be administered for ten days.

*Prevention of Recurrent Attacks of Rheumatic Fever:*

Penicillin or sulfonamides are considered by the American Heart Association 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 by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).<sup>4</sup>

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Erythromycin Delayed-release Capsules, USP and other antibacterial drugs, Erythromycin Delayed-release Capsules, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS**

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, cisapride, pimozide, ergotamine, or dihydroergotamine (see **PRECAUTIONS - Drug Interactions**).

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see **PRECAUTIONS – Drug Interactions**).

**WARNINGS*****Hepatotoxicity***

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

***QT Prolongation***

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

### ***Syphilis in pregnancy***

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration 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.

### ***Clostridium difficile-associated diarrhea***

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Erythromycin Delayed-release Capsules, USP and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### **Drug Interactions**

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (for example, verapamil, amlodipine, diltiazem) (see **PRECAUTIONS, Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS, Drug Interactions**).

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. (See package insert for lovastatin.)

## **PRECAUTIONS**

### **General:**

Prescribing Erythromycin Delayed-release Capsules, USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function (see **CLINICAL PHARMACOLOGY and WARNINGS**).

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

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 percent) 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 percent for infants who took erythromycin for 8 to 14 days and 10 percent for infants who took erythromycin for 15 to 21 days.<sup>5</sup> Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), 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.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

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

### **Information for Patients:**

Patients should be counseled that antibacterial drugs including Erythromycin Delayed-release Capsules, USP should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When Erythromycin Delayed-release Capsules, USP are prescribed to treat a bacterial infection, patients should be told that 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 Delayed-release Capsules, USP or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

### **Drug 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 that when oral erythromycin is given concurrently with theophylline there is a significant decrease in erythromycin serum concentrations of approximately 35 percent. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin

concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

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

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome P450 enzyme system (CYP3A). Co-administration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

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

#### *Ergotamine/dihydroergotamine*

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 central nervous system. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

#### *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.

#### *HMG-CoA Reductase Inhibitors*

Erythromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (for example, lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly (see **CONTRAINDICATIONS**).

#### *Sildenafil (Viagra)*

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

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with carbamazepine, cyclosporine, tacrolimus, alfentanil, disopyramide, bromocriptine, rifabutin, quinidine, methylprednisolone, cilostazol, and vinblastine.

Concomitant administration of erythromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated (see **CONTRAINDICATIONS**).

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QTc interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed (see **CONTRAINDICATIONS**). In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin was co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes, most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported (see **CONTRAINDICATIONS**).

### **Colchicine**

Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

### **Drug/Laboratory test interactions:**

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

### **Carcinogenesis, Mutagenesis and Impairment of Fertility:**

Long-term (2-year) oral studies conducted in rats with erythromycin base did not provide evidence of tumorigenicity. Mutagenicity studies have not been conducted. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25 percent of diet.

### **Pregnancy:**

#### *Teratogenic Effects*

#### *Pregnancy Category B:*

There was no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25 percent of diet) prior to and during mating, during gestation, and through weaning of two successive litters. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery:**

The effect of erythromycin on labor and delivery is unknown.

**Nursing Mothers:**

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

**Pediatric Use:**

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.

**Geriatric Use:**

Clinical studies with Erythromycin Delayed-release Capsules, USP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients (see **WARNINGS**).

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

Erythromycin Delayed-release Capsules, USP 250 mg do not contain sodium or potassium.

**ADVERSE REACTIONS**

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur (see **WARNINGS**). Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see **WARNINGS**).

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsade de pointes (see **WARNINGS**).

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

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

There have been reports of pancreatitis and convulsions.

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

### **OVERDOSAGE**

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

### **DOSAGE AND ADMINISTRATION**

Erythromycin is well absorbed and may be given without regard to meals. Optimum blood levels are obtained in a fasting state (administration at least one half hour and preferably two hours before or after a meal); however, blood levels obtained upon administration of enteric-coated erythromycin products in the presence of food are still above minimal inhibitory concentrations (MICs) of most organisms for which erythromycin is indicated.

#### **ADULTS:**

The usual dose is 250 mg every 6 hours taken one hour before meals. If twice-a-day dosage is desired, the recommended dose is 500 mg every 12 hours. Dosage may be increased up to 4 grams per day, according to the severity of the infection. Twice-a-day dosing is not recommended when doses larger than 1 gram daily are administered.

#### **CHILDREN:**

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

#### **Streptococcal infections:**

A therapeutic dosage of oral erythromycin should be administered for at least 10 days. For continuous prophylaxis against recurrences of streptococcal infections in persons with a history of rheumatic heart disease, the dose is 250 mg twice a day.

#### **Primary syphilis:**

30 to 40 grams given in divided doses over a period of 10 to 15 days.

#### **Intestinal amebiasis:**

250 mg four times daily for 10 to 14 days for adults; 30 to 50 mg/kg/day in divided doses for 10 to 14 days for children.

#### **Legionnaires' disease:**

Although optimal doses have not been established, doses utilized in reported clinical data were those recommended above (1 to 4 grams daily in divided doses).

#### **Urogenital infections during pregnancy due to *Chlamydia trachomatis*:**

Although the optimal dose and duration of therapy have not been established, the suggested treatment is erythromycin 500 mg, by mouth, 4 times a day on an empty stomach for at least 7 days. For women who

cannot tolerate this regimen, a decreased dose of 250 mg, by mouth, 4 times a day should be used for at least 14 days.

For adults with uncomplicated urethral, endocervical, or rectal infections caused by *Chlamydia trachomatis* in whom tetracyclines are contraindicated or not tolerated: 500 mg, by mouth, 4 times a day for at least 7 days.

**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.

**Nongonococcal urethritis due to *Ureaplasma urealyticum*:**

When tetracycline is contraindicated or not tolerated: 500 mg of erythromycin, orally, four times daily for at least 7 days.

**Acute pelvic inflammatory disease due to *N gonorrhoeae*:**

500 mg IV of erythromycin lactobionate for injection, USP every 6 hours for 3 days followed by 250 mg of erythromycin, orally every six hours for 7 days.

**HOW SUPPLIED**

Erythromycin Delayed-release Capsules, USP, are clear and opaque maroon capsules bearing the Product Code ER with pink and yellow particles containing 250 mg of erythromycin supplied in:

Bottles of 100 (NDC 24338-120-13)

**Recommended storage**

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Protect from moisture and excessive heat.

**REFERENCES**

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2. CLSI *Performance Standards for Antimicrobial Susceptibility Testing* – 23rd Informational Supplement, CLSI Document M100-S23, CLSI, 950 West Valley Road, Suite 2500, Wayne, PA 19087 – 2013.
3. CLSI *Performance Standards for Antimicrobial Disk Susceptibility Tests* - 11th Edition Approved Standard CLSI Document M02-A11, CLSI, 950 West Valley Road, Suite 2500, Wayne, PA 19087 – 2012.
4. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart

Association: Prevention of Rheumatic Fever. *Circulation*. 78(4):1082-1086, October 1988.

5. Honein, M.A., et al.: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *The Lancet* 1999;354 (9196): 2101-5.

EDEL-PI-02

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Arbor Pharmaceuticals, LLC

Atlanta, GA 30328



(No. 6301)

## ERYTHROMYCIN TABLETS, USP

Film-coated Tablets

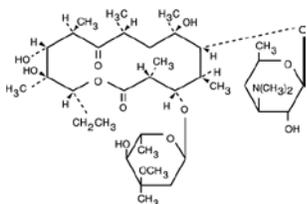
**Rx** only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Erythromycin Tablets and other antibacterial drugs, Erythromycin Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### DESCRIPTION

Erythromycin Tablets, USP are an antibacterial product containing erythromycin, USP, in a unique, nonenteric film coating for oral administration. Erythromycin Tablets are available in two strengths containing either 250 mg or 500 mg of erythromycin base.

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. Erythromycin is a white to off-white powder, slightly soluble in water, and soluble in alcohol, chloroform, and ether. Erythromycin is known chemically as (3R\*, 4S\*, 5S\*, 6R\*, 7R\*, 9R\*, 11R\*, 12R\*, 13S\*, 14R\*)-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl- $\alpha$ -L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-xyllo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione. The molecular formula is  $C_{37}H_{67}NO_{13}$ , and the molecular weight is 733.94. The structural formula is:



### Inactive Ingredients

Colloidal silicon dioxide, croscarmellose sodium, crospovidone, D&C Red No. 30 Aluminum Lake, hydroxypropyl cellulose, hypromellose, hydroxypropyl methylcellulose phthalate, magnesium stearate, microcrystalline cellulose, povidone, polyethylene glycol, propylene glycol, sodium citrate, sodium hydroxide, sorbic acid, sorbitan monooleate, talc, and titanium dioxide.

### CLINICAL PHARMACOLOGY

Orally administered erythromycin base and its salts are readily absorbed in the microbiologically active form. Interindividual variations in the absorption of erythromycin are, however, observed, and some patients do not achieve optimal serum levels. Erythromycin is largely bound to plasma proteins. 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 the passage of the drug across the blood-brain barrier increases in meningitis. Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk. Erythromycin is not removed by peritoneal dialysis or hemodialysis.

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.

Optimal blood levels are obtained when Erythromycin Tablets are given in the fasting state (at least 1/2 hour and preferably 2 hours before meals). Bioavailability data are available from Arbor Pharmaceuticals.

### Microbiology

#### Mechanism of Action

Erythromycin acts by inhibition of protein synthesis by binding 50S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

Mechanism of Resistance

The major route of resistance is modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity while efflux can also be significant.

Interactions with Other Antibiotics

Antagonism exists *in vitro* between erythromycin and clindamycin, lincomycin, and chloramphenicol.

Erythromycin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

**Gram-positive Bacteria:**

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Listeria monocytogenes*

*Staphylococcus aureus* (resistant organisms may emerge during treatment)

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

**Gram-negative Bacteria:**

*Bordetella pertussis*

*Haemophilus influenzae*

*Legionella pneumophila*

*Neisseria gonorrhoeae*

**Other Microorganisms:**

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following bacteria exhibit *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for erythromycin. However, the efficacy of erythromycin in treating clinical infections due to these bacteria has not been established in adequate and well controlled clinical trials.

**Gram-positive Bacteria:**

*Viridans group streptococci*

**Gram-negative Bacteria:**

*Moraxella catarrhalis*

*Susceptibility Test Methods*

When available the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the

physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

**Dilution Techniques:**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method<sup>1,2</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in **Table 1**.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.<sup>2,3</sup> This procedure uses paper disks impregnated with 15 mcg erythromycin to test the susceptibility of microorganisms to erythromycin. The disc diffusion interpretive criteria are provided in **Table 1**.

**Table 1. *In Vitro* Susceptibility Test Interpretive Criteria for Erythromycin**

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i>	≤ 0.5	1-4	≥ 8	≥ 23	14-22	≤ 13
<i>Streptococcus pneumoniae</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15
<i>Streptococcus pyogenes</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15

A report of “Susceptible” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the site of infection necessary to inhibit growth of the pathogen. 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 product 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 antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

**Quality Control:**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1, 2, 3, 4</sup> Standard erythromycin powder should provide the

following range of MIC values noted in **Table 2**. For the diffusion technique using the 15 mcg disk, the criteria in **Table 2** should be achieved.

**Table 2. Acceptable Quality Control Ranges for Erythromycin**

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	22-30
<i>Enterococcus faecalis</i> ATCC 29212	1-4	NA
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03-0.12	25-30

### INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Erythromycin Tablets, USP and other antibacterial drugs, Erythromycin Tablets, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Erythromycin Tablets, USP are indicated in the treatment of infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*; *Streptococcus pneumoniae*; *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower respiratory tract infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Streptococcus pneumoniae*.

Listeriosis caused by *Listeria monocytogenes*.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

Pertussis (whooping cough) caused by *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.

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

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

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythrocin™ Lactobionate- I.V. (erythromycin lactobionate for injection, USP) followed by erythromycin base 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. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

Erythromycins are indicated for treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. 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*.<sup>3</sup>

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.<sup>3</sup>

Primary syphilis caused by *Treponema pallidum*. Erythromycin (oral forms only) is an alternative choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid should be examined before treatment and as part of the follow-up after therapy.

Legionnaires' Disease caused by *Legionella pneumophila*. 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.

## **Prophylaxis**

### *Prevention of Initial Attacks of Rheumatic Fever*

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract e.g., tonsillitis, or pharyngitis).<sup>4</sup> Erythromycin is indicated for the treatment of penicillin-allergic patients. The therapeutic dose should be administered for ten days.

### *Prevention of Recurrent Attacks of Rheumatic Fever*

Penicillin or sulfonamides are considered by the American Heart Association 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 by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).<sup>4</sup>

## **CONTRAINDICATIONS**

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, cisapride, pimozide, ergotamine, or dihydroergotamine. (See **PRECAUTIONS - Drug Interactions**.)

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

## WARNINGS

### *Hepatotoxicity*

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

### *QT Prolongation*

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

### *Syphilis in Pregnancy*

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration 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.

### *Clostridium difficile Associated Diarrhea*

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Erythromycin Tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### *Drug Interactions*

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) (see **PRECAUTIONS - Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS - Drug Interactions**).

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. (See package insert for lovastatin.)

## PRECAUTIONS

## **General**

Prescribing Erythromycin Tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS**.)

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

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.<sup>5</sup> Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal Chlamydia trachomatis infections), 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.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

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

Observational studies in humans have reported cardiovascular malformations after exposure to drug products containing erythromycin during early pregnancy.

## **Information for Patients**

Patients should be counseled that antibacterial drugs including Erythromycin Tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Erythromycin Tablets are prescribed to treat a bacterial infection, patients should be told that 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 Tablets or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

## **Drug 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 that when oral erythromycin is given concurrently with theophylline there is a decrease in erythromycin serum concentrations of approximately 35%. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

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

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

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

#### *Ergotamine/dihydroergotamine*

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. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

*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.

#### *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.

#### *Sildenafil (Viagra)*

Erythromycin has been reported to increase the systemic exposure (AUC) of sildenafil. Reduction of sildenafil dosage should be considered. (See Viagra package insert.) There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methyl-prednisolone, cilostazol, vinblastine, and bromocriptine. Concomitant administration of erythromycin with cisapride, pimozide, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT<sub>c</sub> interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias, have been observed. (See **CONTRAINDICATIONS**.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin was co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes, most likely due to the inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See **CONTRAINDICATIONS**.)

#### *Colchicine*

Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

#### **Drug/Laboratory Test Interactions**

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term oral dietary studies conducted with erythromycin stearate in rats up to 400 mg/kg/day and in mice up to about 500 mg/kg/day (approximately 1 to 2 fold of the maximum human dose on a body surface area basis) did not provide evidence of tumorigenicity. Erythromycin stearate did not show genotoxic potential in the Ames, and mouse lymphoma assays or induce chromosomal aberrations in CHO cells. 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 3 times the maximum human dose on a body surface area basis).

#### **Pregnancy**

##### *Teratogenic Effects*

##### Pregnancy Category B

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body surface area) prior to and during mating, during gestation, and through weaning. 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 and to pregnant rabbits at 125 mg/kg/day (approximately 1 to 3 times the maximum recommended human dose).

#### **Labor and Delivery**

The effect of erythromycin on labor and delivery is unknown.

#### **Nursing Mothers**

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

### **Pediatric Use**

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION**.

### **Geriatric Use**

Elderly patients, particularly those with reduced renal or hepatic function, may be at increased risk for developing erythromycin-induced hearing loss. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. (See **WARNINGS**.)

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

Erythromycin Tablets (250 mg) contain 8.5 mg (0.4 mEq) of sodium per tablet.

Erythromycin Tablets (500 mg) contain 17 mg (0.7 mEq) of sodium per tablet.

The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

### **ADVERSE REACTIONS**

The most frequent side effects of oral erythromycin preparations are gastrointestinal and are dose-related. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Symptoms of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See **WARNINGS**.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. (See **WARNINGS**.)

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

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

There have been rare reports of pancreatitis and convulsions.

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

### **OVERDOSAGE**

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures should be instituted.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

## **DOSAGE AND ADMINISTRATION**

In most patients, Erythromycin Tablets are well absorbed and may be dosed orally without regard to meals. However, optimal blood levels are obtained when Erythromycin Tablets are given in the fasting state (at least 1/2 hour and preferably 2 hours before meals).

### *Adults*

The usual dosage of Erythromycin Tablets is one 250 mg tablet four times daily in equally spaced doses or one 500 mg tablet every 12 hours. Dosage may be increased up to 4 g per day according to the severity of the infection. However, 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 to 50 mg/kg/day, in equally divided doses. For more severe infections this dosage may be doubled but should not exceed 4 g per day.

In the treatment of streptococcal infections of the upper respiratory tract (e.g., tonsillitis or pharyngitis), the therapeutic dosage of erythromycin should be administered for at least ten days.

The American Heart Association suggests a dosage of 250 mg of erythromycin orally, twice a day in long-term prophylaxis of streptococcal upper respiratory tract infections for the prevention of recurring attacks of rheumatic fever in patients allergic to penicillin and sulfonamides.<sup>4</sup>

### **Conjunctivitis of the Newborn Caused by Chlamydia trachomatis**

Oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 2 weeks.<sup>4</sup>

### **Pneumonia of Infancy Caused by Chlamydia trachomatis**

Although the optimal duration of therapy has not been established, the recommended therapy is oral erythromycin suspension 50 mg/kg/day in 4 divided doses for at least 3 weeks.

### **Urogenital Infections During Pregnancy Due to Chlamydia trachomatis**

Although the optimal dose and duration of therapy have not been established, the suggested treatment is 500 mg of erythromycin by mouth four times a day on an empty stomach for at least 7 days. For women who cannot tolerate this regimen, a decreased dose of one erythromycin 500 mg tablet orally every 12 hours or 250 mg by mouth four times a day should be used for at least 14 days.<sup>6</sup>

### **For adults with uncomplicated urethral, endocervical, or rectal infections caused by Chlamydia trachomatis, when tetracycline is contraindicated or not tolerated**

500 mg of erythromycin by mouth four times a day for at least 7 days.<sup>6</sup>

### **For patients with nongonococcal urethritis caused by Ureaplasma urealyticum when tetracycline is contraindicated or not tolerated**

500 mg of erythromycin by mouth four times a day for at least seven days.<sup>6</sup>

### **Primary syphilis**

30 to 40 g given in divided doses over a period of 10 to 15 days.

**Acute Pelvic Inflammatory Disease Caused by *N. gonorrhoeae***

500 mg Erythrocin™ Lactobionate-I.V. (erythromycin lactobionate for injection, USP) every 6 hours for 3 days, followed by 500 mg of erythromycin base orally every 12 hours for 7 days.

**Intestinal Amebiasis**

*Adults*

500 mg every 12 hours or 250 mg every 6 hours for 10 to 14 days.

*Children*

30 to 50 mg/kg/day in divided doses for 10 to 14 days.

**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.

**Legionnaires' Disease**

Although optimal dosage has not been established, doses utilized in reported clinical data were 1 to 4 g daily in divided doses.

**HOW SUPPLIED**

Erythromycin Tablets are supplied as pink, unscored oval tablets in the following strengths and packages.

250 mg tablets (debossed with EB):

Bottles of 30 .....(NDC 24338-102-03)

Bottles of 100.....(NDC 24338-102-13)

500 mg tablets (debossed with EA):

Bottles of 30.....(NDC 24338-104-03)

Bottles of 100.....(NDC 24338-104-13)

**Recommended storage**

Store below 86°F (30°C).

**REFERENCES**

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard – Ninth Edition*. CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-third Informational Supplement*. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.

3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition* CLSI document M02-A11. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
4. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*. 78(4):1082-1086, October 1988.
5. Honein, M.A., et al.: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *The Lancet* 1999;354 (9196): 2101-5.
6. Data on file, Arbor Pharmaceuticals, LLC.

ERB-PI-02      Revised: August 2018  
Arbor Pharmaceuticals, LLC  
Atlanta, GA 30328



# ERYTHROMYCIN ETHYLSUCCINATE TABLETS, USP

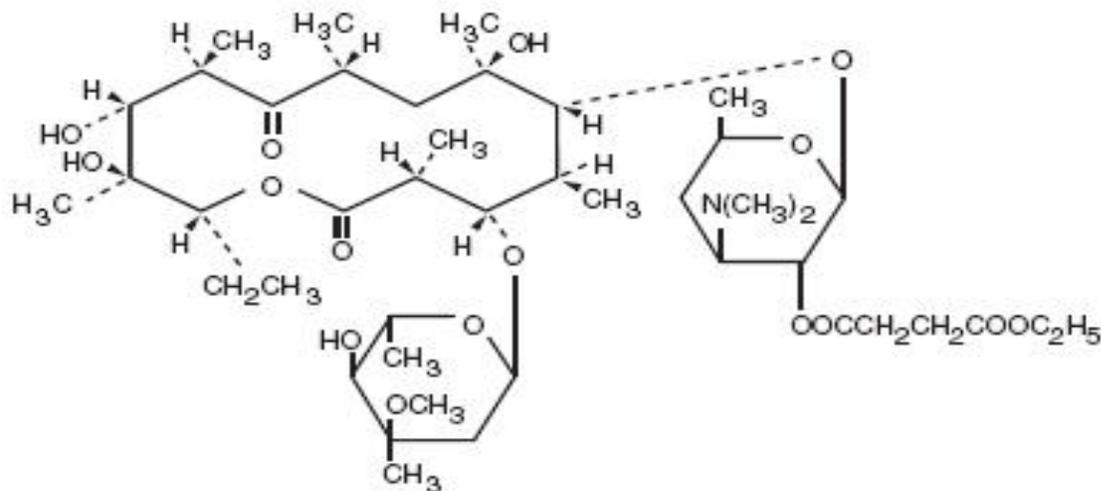
R<sub>x</sub> only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of erythromycin ethylsuccinate tablets and other antibacterial drugs, erythromycin ethylsuccinate tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

## DESCRIPTION

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythraeus*) and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration. Erythromycin ethylsuccinate is known chemically as erythromycin 2'-(ethylsuccinate).

Erythromycin ethylsuccinate tablets, USP for oral administration are intended primarily for adults or older children. Each tablet contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin activity. The molecular formula is  $C_{43}H_{75}NO_{16}$  and the molecular weight is 862.06. The structural formula is:



## Inactive Ingredients:

Confectioner's sugar (contains corn starch), corn starch, FD&C Red No. 40, magnesium stearate, polacrillin potassium and sodium citrate.

## CLINICAL PHARMACOLOGY

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

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. 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 of erythromycin is excreted in active form in the urine.

Erythromycin crosses the placental barrier, but fetal plasma levels are low. The drug is excreted in human milk.

## **Microbiology**

### Mechanism of Action

Erythromycin acts by inhibition of protein synthesis by binding 50S ribosomal subunits of susceptible organisms. It does not affect nucleic acid synthesis.

### Resistance

The major route of resistance is modification of the 23S rRNA in the 50S ribosomal subunit to insensitivity while efflux can also be significant.

### Interactions With Other Antimicrobials

Antagonism exists in vitro between erythromycin and clindamycin, lincomycin, and chloramphenicol.

### Antimicrobial Activity

Erythromycin has been shown to be active against most isolates of the following microorganisms both in vitro and in clinical infections [see *Indications and Usage (1)*].

#### Aerobic bacteria

Gram-positive bacteria:

*Corynebacterium diphtheriae*

*Corynebacterium minutissimum*

*Listeria monocytogenes*

*Staphylococcus aureus* (resistant organisms may emerge during treatment)

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

Gram-negative bacteria:

*Bordetella pertussis*

*Haemophilus influenzae*

*Legionella pneumophila*

*Neisseria gonorrhoeae*

#### Other microorganisms:

*Chlamydia trachomatis*

*Entamoeba histolytica*

*Mycoplasma pneumoniae*

*Treponema pallidum*

*Ureaplasma urealyticum*

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for erythromycin against isolates of similar genus or organism group. However, the efficacy of erythromycin in treating clinical infections caused by these bacteria has not been established in adequate and well controlled clinical trials.

**Aerobic bacteria**

Gram-positive bacteria:

*Viridans group streptococci*

Gram-negative bacteria:

*Moraxella catarrhalis*

**Susceptibility Test Methods**

When available the clinical microbiology laboratory should provide cumulative reports of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid in the selection of an appropriate antibacterial drug for treatment.

*Dilution Techniques*

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method<sup>1,2</sup> (broth and/or agar). The MIC values should be interpreted according to criteria provided in Table 1.

*Diffusion techniques*

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.<sup>2,3</sup> This procedure uses paper disks impregnated with 15 mcg erythromycin to test the susceptibility of microorganisms to erythromycin. The disc diffusion interpretive criteria are provided in Table 1.

**Table 1. Susceptibility Test Interpretive Criteria for Erythromycin**

<b>Pathogen</b>	<b>Minimum Inhibitory Concentrations (mcg/mL)</b>			<b>Disk Diffusion (zone diameters in mm)</b>		
	<b>S</b>	<b>I</b>	<b>R</b>	<b>S</b>	<b>I</b>	<b>R</b>
<i>Staphylococcus aureus</i>	≤ 0.5	1-4	≥ 8	≥ 23	14-22	≤ 13
<i>Streptococcus pneumoniae</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15
<i>Streptococcus pyogenes</i>	≤ 0.25	0.5	≥ 1	≥ 21	16-20	≤ 15

A report of *Susceptible (S)* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the site of infection.

A report of *Intermediate (I)* 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 a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation.

A report of *Resistant (R)* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

### Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1, 2, 3</sup> Standard erythromycin powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 15 mcg disk, the criteria in Table 2 should be achieved.

**Table 2. Acceptable Quality Control Ranges for Erythromycin**

	<b>Minimum Inhibitory Concentrations (mcg/mL)</b>	<b>Disk Diffusion (zone diameters in mm)</b>
<i>Staphylococcus aureus</i> ATCC 29213	0.25-1	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	22-30
<i>Enterococcus faecalis</i> ATCC 29212	1-4	NA
<i>Streptococcus pneumoniae</i> ATCC 49619	0.03-0.12	25-30

### **INDICATIONS AND USAGE**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of erythromycin ethylsuccinate tablets, USP and other antibacterial drugs, erythromycin ethylsuccinate tablets, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Erythromycin ethylsuccinate tablets, USP are indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below:

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* (when used concomitantly with adequate doses of sulfonamides, since many strains of *H. influenzae* are not susceptible to

the erythromycin concentrations ordinarily achieved). (See appropriate sulfonamide labeling for prescribing information.)

Lower-respiratory tract infections of mild to moderate severity caused by *Streptococcus pneumoniae* or *Streptococcus pyogenes*.

Listeriosis caused by *Listeria monocytogenes*.

Pertussis (whooping cough) caused by *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.

Respiratory tract infections due to *Mycoplasma pneumoniae*.

Skin and skin structure infections of mild to moderate severity caused by *Streptococcus pyogenes* or *Staphylococcus aureus* (resistant staphylococci may emerge during treatment).

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

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

Intestinal amebiasis caused by *Entamoeba histolytica* (oral erythromycins only). Extraenteric amebiasis requires treatment with other agents.

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: 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. Patients should have a serologic test for syphilis before receiving erythromycin as treatment of gonorrhea and a follow-up serologic test for syphilis after 3 months.

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

Erythromycins are indicated for the treatment of the following infections caused by *Chlamydia trachomatis*: conjunctivitis of the newborn, pneumonia of infancy, and urogenital infections during pregnancy. 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*.

When tetracyclines are contraindicated or not tolerated, erythromycin is indicated for the treatment of nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Legionnaires' Disease caused by *Legionella pneumophila*. 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.

### **Prophylaxis:**

#### *Prevention of Initial Attacks of Rheumatic Fever*

Penicillin is considered by the American Heart Association to be the drug of choice in the prevention of initial attacks of rheumatic fever (treatment of *Streptococcus pyogenes* infections of the upper respiratory tract, e.g., tonsillitis or pharyngitis). Erythromycin is indicated for the treatment of penicillin-allergic patients.<sup>4</sup> The therapeutic dose should be administered for 10 days.

#### *Prevention of Recurrent Attacks of Rheumatic Fever*

Penicillin or sulfonamides are considered by the American Heart Association 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 by the American Heart Association in the long-term prophylaxis of streptococcal pharyngitis (for the prevention of recurrent attacks of rheumatic fever).<sup>4</sup>

## CONTRAINDICATIONS

Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

Erythromycin is contraindicated in patients taking terfenadine, astemizole, pimozide, or cisapride. (See **PRECAUTIONS** - *Drug Interactions*.)

Do not use erythromycin concomitantly with HMG CoA reductase inhibitors (statins) that are extensively metabolized by CYP 3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

## WARNINGS

### *Hepatotoxicity*

There have been reports of hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, occurring in patients receiving oral erythromycin products.

### *QT Prolongation*

Erythromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving erythromycin. Fatalities have been reported. Erythromycin should be avoided in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

### *Syphilis in Pregnancy*

There have been reports suggesting that erythromycin does not reach the fetus in adequate concentration 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.

### *Clostridium difficile Associated Diarrhea*

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Erythromycin Ethylsuccinate Tablets, USP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical

history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

#### *Drug Interactions*

Serious adverse reactions have been reported in patients taking erythromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) (see **PRECAUTIONS-Drug Interactions**).

There have been post-marketing reports of colchicine toxicity with concomitant use of erythromycin and colchicine. This interaction is potentially life-threatening, and may occur while using both drugs at their recommended doses (see **PRECAUTIONS-Drug Interactions**).

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. (See package insert for lovastatin.)

## **PRECAUTIONS**

### **General**

Prescribing erythromycin ethylsuccinate tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Since erythromycin is principally excreted by the liver, caution should be exercised when erythromycin is administered to patients with impaired hepatic function. (See **CLINICAL PHARMACOLOGY** and **WARNINGS** sections.)

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

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.<sup>5</sup> Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or neonatal *Chlamydia trachomatis* infections), 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.

Prolonged or repeated use of erythromycin may result in an overgrowth of nonsusceptible bacteria or fungi. If superinfection occurs, erythromycin should be discontinued and appropriate therapy instituted.

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

### **Information for Patients**

Patients should be counseled that antibacterial drugs including erythromycin ethylsuccinate tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When erythromycin ethylsuccinate tablets is prescribed to treat a bacterial infection, patients should be told that 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 ethylsuccinate tablets or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

### **Drug 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 that when oral erythromycin is given concurrently with theophylline there is a decrease in erythromycin serum concentrations of approximately 35%. The mechanism by which this interaction occurs is unknown. The decrease in erythromycin concentrations due to co-administration of theophylline could result in subtherapeutic concentrations of erythromycin.

#### *Verapamil*

Hypotension, bradyarrhythmias, and lactic acidosis have been observed in patients receiving concurrent verapamil, belonging to the calcium channel blockers drug class.

#### *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 oral anticoagulants were used concomitantly. Increased anticoagulation effects due to interactions of erythromycin with various oral anticoagulants may be more pronounced in the elderly.

Erythromycin is a substrate and inhibitor of the 3A isoform subfamily of the cytochrome p450 enzyme system (CYP3A). Coadministration of erythromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving erythromycin.

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

*Ergotamine/dihydroergotamine*

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. Concomitant administration of erythromycin with ergotamine or dihydroergotamine is contraindicated (see **CONTRAINDICATIONS**).

*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.

*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.

*Sildenafil (Viagra)*

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

There have been spontaneous or published reports of CYP3A based interactions of erythromycin with cyclosporine, carbamazepine, tacrolimus, alfentanil, disopyramide, rifabutin, quinidine, methylprednisolone, cilostazol, vinblastine, and bromocriptine.

Concomitant administration of erythromycin with cisapride, pimozone, astemizole, or terfenadine is contraindicated. (See **CONTRAINDICATIONS**.)

In addition, there have been reports of interactions of erythromycin with drugs not thought to be metabolized by CYP3A, including hexobarbital, phenytoin, and valproate.

Erythromycin has been reported to significantly alter the metabolism of the nonsedating antihistamines terfenadine and astemizole when taken concomitantly. Rare cases of serious cardiovascular adverse events, including electrocardiographic QT/QT<sub>c</sub> interval prolongation, cardiac arrest, torsades de pointes, and other ventricular arrhythmias have been observed. (See **CONTRAINDICATIONS**.) In addition, deaths have been reported rarely with concomitant administration of terfenadine and erythromycin.

There have been post-marketing reports of drug interactions when erythromycin is co-administered with cisapride, resulting in QT prolongation, cardiac arrhythmias, ventricular tachycardia, ventricular fibrillation, and torsades de pointes, most likely due to inhibition of hepatic metabolism of cisapride by erythromycin. Fatalities have been reported. (See **CONTRAINDICATIONS**.)

*Colchicine*

Colchicine is a substrate for both CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Erythromycin is considered a moderate inhibitor of CYP3A4. A significant increase in colchicine plasma concentration is anticipated when co-administered with moderate CYP3A4 inhibitors such as erythromycin. If co-administration of colchicine and erythromycin is necessary, the starting dose of colchicine may need to be reduced, and the maximum colchicine

dose should be lowered. Patients should be monitored for clinical symptoms of colchicine toxicity (see **WARNINGS**).

**Drug/Laboratory Test Interactions:**

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

Long-term oral dietary studies conducted with erythromycin stearate in rats up to 400 mg/kg/day and in mice up to about 500 mg/kg/day (approximately 1 to 2 fold of the maximum human dose on a body surface area basis) did not provide evidence of tumorigenicity. Erythromycin stearate did not show genotoxic potential in the Ames, and mouse lymphoma assays or induce chromosomal aberrations in CHO cells. 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 3 times the maximum human dose on a body surface area basis).

**Pregnancy:**

*Teratogenic Effects*

Pregnancy Category B:

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body surface area) prior to and during mating, during gestation, and through weaning.

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 and to pregnant rabbits at 125 mg/kg/day (approximately 1 to 3 times the maximum recommended human dose).

**Labor and Delivery:**

The effect of erythromycin on labor and delivery is unknown.

**Nursing Mothers:**

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

**Pediatric Use:**

See **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections.

**Geriatric Use:**

Elderly patients, particularly those with reduced renal or hepatic function, may be at increased risk for developing erythromycin-induced hearing loss. (See **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**.)

Elderly patients may be more susceptible to the development of torsades de pointes arrhythmias than younger patients. (See **WARNINGS**.)

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

Erythromycin Ethylsuccinate Tablets (400 mg) contain 47 mg (2 mEq) of sodium and 9.2 mg (0.3 mEq) of potassium per tablet.

The geriatric population may respond with a blunted natriuresis to salt loading. This may be clinically important with regard to such diseases as congestive heart failure.

**ADVERSE REACTIONS**

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

of hepatitis, hepatic dysfunction and/or abnormal liver function test results may occur. (See **WARNINGS** section.)

Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS** section.)

Erythromycin has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes. (See **WARNINGS**.)

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

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

There have been rare reports of pancreatitis and convulsions.

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

### **OVERDOSAGE**

In case of overdosage, erythromycin should be discontinued. Overdosage should be handled with the prompt elimination of unabsorbed drug and all other appropriate measures should be instituted.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

### **DOSAGE AND ADMINISTRATION**

Erythromycin ethylsuccinate tablets may be administered without regard to meals. To avoid unpleasant taste, the 400 mg tablets should not be chewed.

#### *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 6 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 by administering one-third of the total daily dose every 8 hours.

The following dosage schedule is suggested for mild to moderate infections:

<b>Body Weight</b>	<b>Total Daily Dose</b>
Under 10 lbs	30 to 50 mg/kg/day 15 to 25 mg/lb/day
10 to 15 lbs	200 mg
16 to 25 lbs	400 mg
26 to 50 lbs	800 mg
51 to 100 lbs	1200 mg
over 100 lbs	1600 mg

#### *Adults*

400 mg 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.

For adult dosage calculation, use a ratio of 400 mg of erythromycin activity as the ethylsuccinate to 250 mg of erythromycin activity as the stearate, base or estolate.

In the treatment of streptococcal infections, a therapeutic dosage of 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 Treatment of Urethritis Due to *C. trachomatis* or *U. urealyticum***

800 mg three times a day for 7 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 Amebiasis**

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 Legionnaires' Disease**

Although optimal doses have not been established, doses utilized in reported clinical data were those recommended above (1.6 to 4 g daily in divided doses.)

**HOW SUPPLIED**

Erythromycin ethylsuccinate Tablets, USP, 400 mg are supplied as mottled pink, oval tablets bearing the Code 74 ZE in:

Bottles of 30 (NDC 24338 -110-03)

Bottles of 100 (NDC 24338 -110-13).

**Recommended storage**

Protect tablets from exposure to light and moisture. Store below 86°F (30°C).

**REFERENCES**

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2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing. 27<sup>th</sup> ed.* CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard - Twelfth Edition*. CLSI document M02-A12. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.
4. Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association: Prevention of Rheumatic Fever. *Circulation*. 78(4):1082-1086, October 1988.
5. Honein, M.A., et al.: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *The Lancet* 1999;354 (9196): 2101-5.
6. Data on file, Arbor Pharmaceuticals, LLC.

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