EN-3199

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ERYTHROCIN™ Lactobionate - IV
Erythromycin Lactobionate for Injection, USP
Single-dose ADD-Vantage™ Vials
For Intravenous Use Only

Rx only

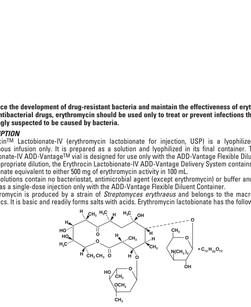
To reduce the development of drug-resistant bacteria and maintain the effectiveness of erythromycin and other antibacterial drugs, erythromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Erythrocin™ Lactobionate-IV (erythromycin lactobionate for injection, USP) is a lyophilized powder for intravenous infusion only. It is prepared as a solution and lyophilized in its final container. The Erythrocin Lactobionate-IV ADD-Vantage™ Vial is designed for use only with the ADD-Vantage Flexible Diluent Container. After appropriate dilution, the Erythrocin Lactobionate-IV ADD-Vantage Delivery System contains erythromycin lactobionate equivalent to either 500 mg of erythromycin or 1000 mg of erythromycin in 100 ml.

The solutions contain no bacteriostat, antimicrobial agent (except erythromycin) or buffer and are intended for use as a single-dose injection only with the ADD-Vantage Flexible Diluent Container.

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. Erythromycin lactobionate has the following structure:



CLINICAL PHARMACOLOGY

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 and is excreted in breast 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. From 12 to 15 percent of intravenously administered erythromycin is excreted in active form in the urine.

Intravenous infusion of 500 mg of erythromycin lactobionate at a constant rate over 1 hour in fasting adults produced a mean serum erythromycin level of approximately 7 mcg/ml, at 20 minutes, 10 mcg/ml, at 1 hour, 2.6 mcg/ml, at 2.5 hours, and 1 mcg/ml, at 6 hours.

Microbiology

Erythromycin is a macrolide antibiotic with activity against Gram-positive and Gram-negative bacteria.

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.

Interactions with Other Antibiotics

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

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

Development of Resistance

Resistance to erythromycin in *S. aureus* may emerge during therapy.

Erythromycin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections (see *INDICATIONS AND USAGE*):

Gram-positive bacteria Aerobic

Corynebacterium diphtheriae
Corynebacterium minutissimum
Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-negative bacteria

Legionella pneumophila
Neisseria gonorrhoeae

Other Microorganisms

Mycoplasma pneumonia

At least 90 percent of the following microorganisms exhibit an *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 microorganisms has not been established in adequate and well-controlled trials.

Gram-negative bacteria

Moraxella catarrhalis

Susceptibility Testing

When available, the clinical microbiology laboratory should provide cumulative results of the *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 the most effective antimicrobial.

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 procedure. Standardized procedures are based on a dilution method (broth or agar)[1] or equivalent with standardized inoculum concentrations and standardized concentrations of erythromycin powder. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 mcg of erythromycin to test the susceptibility of microorganisms to erythromycin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility Interpretive Criteria for Erythromycin

	Susceptibility Interpretive Criteria					
	Minimum Inhibitory Concentration (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Staphylococcus spp.	≤0.5	1 to 4	≥8	≥23	14 to 22	≤13
Enterococcus spp.	≤0.5	1 to 4	≥8	≥23	14 to 22	≤13
Streptococcus pneumoniae[a,b]	≤0.25	0.5	≥1	≥21	16 to 20	≤15
Streptococcus spp. (β-hemolytic group)[b,c]	≤0.25	0.5	≥1	≥21	16 to 20	≤15
Streptococcus spp. (Viridans group)[b,c]	≤0.25	0.5	≥1	≥21	16 to 20	≤15

[a] The MIC interpretive criteria for *Streptococcus pneumoniae*, *Streptococcus* spp. (β-hemolytic group), and *Streptococcus* spp. (Viridans group) are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth supplemented with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35 ± 2°C for 20 to 24 hours.

[b] The zone diameter interpretive criteria for *Streptococcus pneumoniae*, *Streptococcus* spp. (β-hemolytic group), and *Streptococcus* spp. (Viridans group) are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35 ± 2°C for 20 to 24 hours.

A report of *Susceptible* indicates that the antimicrobial is likely to inhibit growth of the pathogen 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 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 in the blood reaches the concentrations usually achievable and other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures[2]. Standard Erythromycin powder should provide the following range of values noted in Table 2.

Table 2. Acceptable Quality Control Ranges for Erythromycin

	Acceptable Quality Control Ranges		
QC Strain	Minimum Inhibitory Concentration (mcg/mL)	Disk Diffusion (zone diameter in mm)	
Enterococcus faecalis ATCC 29212	1 to 4	NA[a]	
Staphylococcus aureus ATCC 29213	0.25 to 1	NA	
Staphylococcus aureus ATCC 25923	NA	22 to 30	
Streptococcus pneumoniae ATCC 49619[b]	0.03 to 0.12[c]	25 to 30[d]	

[a] not applicable

[b] This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

[c] This quality control range for *S. pneumoniae* is applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth supplemented with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35 ± 2°C for 20 to 24 hours.

[d] This quality control zone diameter range is applicable only to tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35 ± 2°C for 20 to 24 hours.

INDICATIONS AND USAGE

Erythrocin Lactobionate-IV (erythromycin lactobionate for injection, USP) is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the diseases listed below when oral administration is not possible or when the severity of the infection requires immediate high serum levels of erythromycin. Parenteral erythromycin therapy should be replaced as soon as oral administration at the appropriate time.

Upper respiratory tract infections of mild to moderate degree caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci). *Streptococcus* species (*Viridans streptococci*), *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* (Group A beta-hemolytic streptococci), *Streptococcus pneumoniae* (*Diplococcus pneumoniae*).

Respiratory tract infections due to *Mycoplasma pneumoniae*.

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

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

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

Acute pelvic inflammatory disease caused by *Neisseria gonorrhoeae*: Erythrocin Lactobionate-IV (erythromycin lactobionate for injection, USP) followed by erythromycin stearate or 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.

Before treatment of gonorrhea, patients who are suspected of also having syphilis should have a microscopic examination for *T. pallidum* (by immunofluorescence or darkfield) before receiving erythromycin and monthly serologic tests for a minimum of 4 months thereafter.

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.

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 Group A beta-hemolytic streptococcal infections of the upper respiratory tract e.g., tonsillitis, or pharyngitis).[4] 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.[4]

Prevention of Bacterial Endocarditis

Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been recommended by the American Heart Association for prevention of bacterial endocarditis in penicillin-allergic patients with prosthetic cardiac valves, most congenital cardiac malformations, surgically constructed systemic pulmonary shunts, rheumatic or other acquired valvular dysfunction, idiopathic hypertrophic subaortic stenosis (IHSS), previous history of bacterial endocarditis and mitral valve prolapse with insufficiency when they undergo dental procedures and surgical procedures of the upper respiratory tract.[5]

To reduce the development of drug-resistant bacteria and maintain the effectiveness of erythromycin and other antibacterial drugs, erythromycin 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 or astemizole. (See *PRECAUTIONS – Drug Interactions*).

WARNINGS

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

***Clostridium difficile* associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including erythromycin, 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.

Life-threatening episodes of ventricular tachycardia associated with prolonged QT interval (torsades de pointes) have been reported in some patients after intravenous administration of erythromycin lactobionate.

Susceptibility to the development of torsades de pointes arrhythmias, a rare but serious cardiac condition, is related to electrolyte imbalance, hepatic dysfunction, myocardial ischemia, left ventricular dysfunction, idiopathic Q-T prolongation, and concurrent arrhythmic therapy.[1] Elderly patients exhibit a greater frequency of decreased hepatic function, cardiac function, and of concomitant disease and other drug therapy, and therefore should be monitored carefully during Erythrocin™ therapy.

PRECAUTIONS

General

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*).

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

Prolonged or repeated use of erythromycin may result in an overgrowth of non-susceptible 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.

Prescribing erythromycin 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.

Laboratory Tests

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Drug Interactions

Erythromycin use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

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

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

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

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

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.

The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P450 system may be associated with elevations in serum levels of these other drugs. Examples have been reports of elevations of benzodiazepines, vinblastine, vincristine, and astemizole, plasmin concentrations of digitoxin metabolized by the gut flora, and reduced clearance of theophylline, carbamazepine, cyclosporine, terfenadine, triazolam, and oral anticoagulants (e.g., warfarin) in patients receiving erythromycin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate carcinogenic potential. Mutagenicity studies have been conducted using erythromycin base and have yielded negative results. Erythromycin has been reported to adversely affect spermatogenesis in animal studies.

Pregnancy

Pregnancy Category B

Erythromycin crosses the placental barrier and has been reported to cause hypertrophic pyloric stenosis in infants born to women receiving oral erythromycin during late pregnancy. (See *ADVERSE REACTIONS*).

Reproduction studies have been performed using erythromycin base (as stearate) at doses up to 2 times the human daily oral dose and have revealed no evidence of impairment of fertility or harm to the fetus due to erythromycin base. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, erythromycin base should be used during pregnancy only if the potential benefit justifies the potential fetal risk.

Nursing Mothers

The effect of erythromycin on labor and delivery is unknown.

Pediatric Use

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

Geriatric Use

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*).

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

Prolonged or repeated use of erythromycin may result in an overgrowth of non-susceptible 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.

Prescribing erythromycin 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.

Laboratory Tests

Erythromycin interferes with the fluorometric determination of urinary catecholamines.

Drug Interactions

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a. To remove the vial from cover, grasp the tab over the vial and pull off in the direction of the arrow. Pull up to break the seal. (See FIGURE 1)

b. Remove the vial from the foil pouch and place it on a flat surface. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. Tighten by hand only. Do not use a wrench or other device. (See FIGURE 2)

c. Screw the vial into the inlet port of the diluent container until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. Tighten by hand only. Do not use a wrench or other device. (See FIGURE 2)

NOTE: Vial must be screwed in tightly to assure a seal. Do not attempt to remove. (See FIGURE 4)

FIGURE 1

FIGURE 2

d. Squeeze the diluent container firmly to break the seal between the vial stopper and the diluent container. (See FIGURE 3)

e. Mix the diluent and the vial by inverting the container and squeezing the lower portion of the container. (See FIGURE 4)

f. Delicately shake the vial to assure that it is safe by trying to turn it further by hand in the direction of assembly.

To Reconstitute the Drug:

a. Select appropriately sized syringe and needle for withdrawal of the required amount of diluent.

b. Remove the diluent container from the foil pouch and place it on a flat surface.

c. Remove the cover from the port of the diluent container by pulling the tab over the port. (See FIGURE 5)

d. Insert the needle of the syringe into the port and inject the diluent into the vial. (See FIGURE 6)

e. Shake the vial to assure that it is safe by trying to turn it further by hand in the direction of assembly.

f. Delicately shake the container to assure that the drug is dissolved. (See FIGURE 7)

g. Remove the syringe and needle from the port of the diluent container by pulling the tab over the port. (See FIGURE 8)

h. Remove the diluent container from the foil pouch and place it on a flat surface.

i. Remove the cover from the port of the diluent container by pulling the tab over the port. (See FIGURE 5)

j. Insert the needle of the administration set into the port and tighten by hand only. Do not use a wrench or other device. (See FIGURE 9)

k. Invert the diluent container and the vial. Delicately shake the container to assure that the drug is dissolved. (See FIGURE 7)

l. Squeeze the lower portion of the diluent container firmly to break the seal between the vial stopper and the diluent container. (See FIGURE 4)

m. Remove the diluent container from the vial. Delicately shake the container to assure that the drug is dissolved. (See FIGURE 7)

n. Remove the diluent container from the vial. Delicately shake the container to assure that the drug is dissolved. (See FIGURE 7)

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