

ERYTHROCIN[®] LACTOBIONATE-I.V.

(sterile erythromycin lactobionate)

ADD-Vantage[®] Vials Single Dose R_x only

For Intravenous Use Only

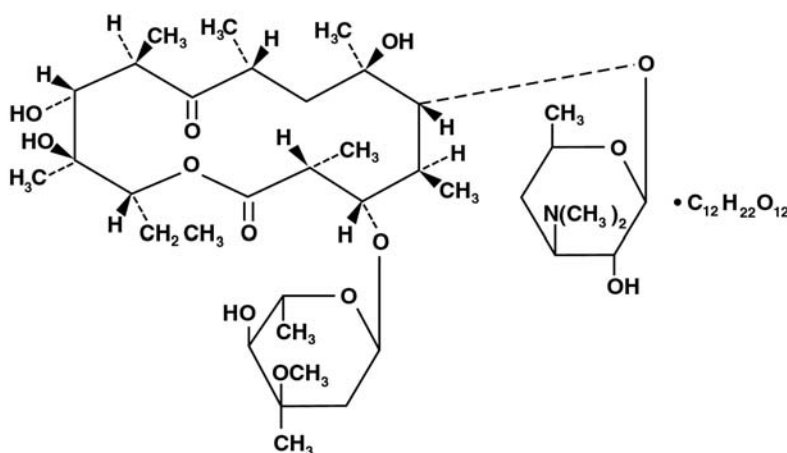
To reduce the development of drug-resistant bacteria and maintain the effectiveness of erythromycin and other antibacterial drugs, erythromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Erythrocin[®] Lactobionate-I.V. (sterile erythromycin lactobionate) is a lyophilized powder for intravenous infusion only. It is prepared as a solution and lyophilized in its final container. The Erythrocin Lactobionate-I.V. ADD-Vantage[®] vial is designed for use only with the ADD-Vantage Flexible Diluent Container. After appropriate dilution, the Erythrocin Lactobionate-I.V. ADD-Vantage Delivery System contains erythromycin lactobionate equivalent to either 500 mg of erythromycin activity in 100 mL or 1 g erythromycin activity in 250 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 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 together.

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

Erythromycin is usually active against the following organisms *in vitro* (prior to use, refer to **INDICATIONS AND USAGE** section):

Gram-positive Bacteria: Staphylococcus aureus (resistant organisms may emerge during treatment), Streptococcus pyogenes (Group A beta-hemolytic streptococcus), Alpha-hemolytic streptococcus (viridans group), Streptococcus (diplococcus) pneumoniae, Corynebacterium diphtheriae, Corynebacterium minutissimum.

Gram-negative Bacteria: Neisseria gonorrhoeae, Legionella pneumophila, Bordetella pertussis.

Mycoplasma: Mycoplasma pneumoniae, Ureaplasma urealyticum.

Other Microorganisms: Chlamydia trachomatis, Entamoeba histolytica, Treponema pallidum, Listeria monocytogenes.

Susceptibility Testing:

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such standardized single-disc procedure has been recommended for use with discs to test susceptibility to erythromycin.¹ Interpretation involves correlation of the zone diameters obtained in the disc test with minimal inhibitory concentration (MIC) values for erythromycin.

Reports from the laboratory giving results of the standardized single-disc susceptibility test using a 15 mcg erythromycin disc should be interpreted according to the following criteria:

Susceptible organisms produce zones of 18 mm or greater, indicating that the tested organism is likely to respond to therapy.

Resistant organisms produce zones of 13 mm or less, indicating that other therapy should be selected.

Organisms of intermediate susceptibility produce zones of 14 to 17 mm. The “intermediate” category provides a “buffer zone” which should prevent small, uncontrolled technical factors from causing major discrepancies in interpretations; thus, when a zone diameter falls within the “intermediate” range, the results may be considered equivocal. If alternative drugs are not available, confirmation by dilution tests may be indicated.

Standardized procedures require the use of control organisms. The 15 mcg erythromycin disc should give zone diameters between 22 and 30 mm for the *S. aureus* ATCC 25923 control strain.

A bacterial isolate may be considered susceptible if the MIC value² for erythromycin is not more than 2 mcg/mL. Organisms are considered resistant if the MIC is 8 mcg/mL or higher. The MIC of erythromycin for *S. aureus* ATCC 29213 control strain should be between 0.12 and 0.5 mcg/mL.

INDICATIONS AND USAGE

Erythrocin Lactobionate-I.V. (sterile erythromycin lactobionate) 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. Intravenous therapy should be replaced by 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 pneumoniae* (*Diplococcus 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* (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 infections due 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-I.V. (sterile erythromycin lactobionate) followed by erythromycin stearate or 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).³ 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).³

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.⁴

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.

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** sections.)

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 the elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin with carbamazepine, cyclosporine, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin bromocriptine, valproate, terfenadine, and astemizole. Serum concentrations of drugs metabolized by the cytochrome P450 system should be monitored closely in patients concurrently receiving erythromycin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal data with erythromycin lactobionate for use in determination of possible carcinogenic effects are not available. However, long-term oral studies in rats with erythromycin ethylsuccinate and 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% of diet.

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

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

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

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

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

ADVERSE REACTIONS

Side effects following the use of intravenous erythromycin are rare. Occasional venous irritation has been encountered, but if the infusion is given slowly, in dilute solution, preferably by continuous intravenous infusion or intermittent infusion in no less than 20 to 60 minutes, pain and vessel trauma are minimized.

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

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

OVERDOSAGE

In the case of overdosage, erythromycin infusion should be discontinued.

Erythromycin is not removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

For the treatment of severe infections in adults and children, the recommended intravenous dose of erythromycin lactobionate is 15 to 20 mg/kg/day. Higher doses, up to 4 g/day, may be given for severe infections. Erythrocin Lactobionate-I.V. (sterile erythromycin lactobionate) in the ADD-Vantage system should be administered by intermittent intravenous infusion. Due to the irritative properties of erythromycin, I.V. push is an unacceptable route of administration.

Continuous infusion of erythromycin lactobionate has been preferred due to the slower infusion rate and lower concentration of erythromycin; however, intermittent infusion at six hour intervals is effective. Intravenous erythromycin should be replaced by oral erythromycin as soon as possible.

The drug should be administered as a single dose from the ADD-Vantage flexible diluent container. Discard any unused portion.

For intermittent infusion: administer one-fourth the total daily dose of erythromycin lactobionate by intravenous infusion in 20 to 60 minutes at intervals not greater than every six hours. The final diluted solution of erythromycin lactobionate is prepared to give a concentration of 1 to 5 mg/mL. No less than 100 mL of I.V. diluent should be used. Infusion should be sufficiently slow to minimize pain along the vein.

For treatment of acute pelvic inflammatory disease caused by *N. Gonorrhoeae*. In female patients hypersensitive to penicillins, administer 500 mg erythromycin lactobionate every six hours for three days, followed by oral administration of 250 mg erythromycin stearate or base every six hours for seven days.

For treatment of Legionnaires' Disease: Although optimal doses have not been established, doses utilized in reported clinical data were 1 to 4 grams daily in divided doses.

In the treatment of Group A beta-hemolytic streptococcal infections of the upper respiratory tract (e.g., tonsillitis or pharyngitis), the therapeutic dosage of erythromycin should be administered for 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.³

In prophylaxis against bacterial endocarditis (see **INDICATIONS AND USAGE** section) the oral regimen for penicillin allergic patients is erythromycin 1 gram, 1 hour before the procedure followed by 500 mg six hours later.⁴

Preparation of Solution:

The Erythrocin Lactobionate-I.V. ADD-Vantage vial may be used with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP in the ADD-Vantage flexible diluent container. The 500 mg and 1 g ADD-Vantage vials must be used as single doses with the 100 mL and 250 mL ADD-Vantage flexible diluent containers, respectively. The resulting solutions will contain erythromycin activity equal to approximately 5 mg/mL and 4 mg/mL, respectively.

Do not administer unless solution is clear and container is undamaged. Discard any unused portion.

INSTRUCTIONS FOR USE

To Use Vial in ADD-Vantage Flexible Diluent Container

To Open:

Peel overwrap at corner and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container:

(Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
 - a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (See FIGURE 1.), then pull straight up to remove the cap. (See FIGURE 2.) **NOTE:** Do not access vial with syringe.

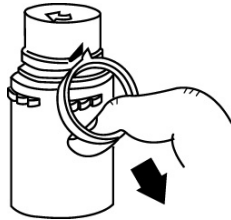


Fig. 1



Fig. 2

- b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (See FIGURE 3.)
2. Screw the vial into the vial port until it will go no further. **THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL.** This occurs approximately 1/2 turn (180°) after the first audible click. (See FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go.

NOTE: Once vial is seated, do not attempt to remove. (See FIGURE 4.)



Fig. 3

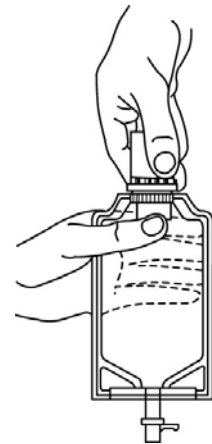


Fig. 4

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

To Reconstitute the Drug:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (See FIGURE 5.)
3. Pull the inner cap from the drug vial. (See FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.

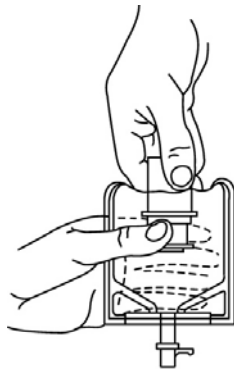


Fig. 5

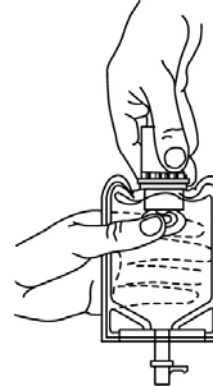


Fig. 6

Preparation for Administration:

(Use Aseptic Technique)

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.

NOTE: See full directions on administration set carton.

6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible containers in series connections.

Stability:

In 0.9% Sodium Chloride Injection, USP

The final diluted solution of erythromycin lactobionate should be completely administered **within 8 hours** in order to assure proper potency.

In 5% Dextrose Injection, USP

The final diluted solution of erythromycin lactobionate should be completely administered **within 2 hours** in order to assure proper potency.

No drug or chemical agent should be added to an Erythrocin Lactobionate-I.V. fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

WARNING: Do not use flexible container in series connections.

HOW SUPPLIED

Erythrocin Lactobionate-I.V. (sterile erythromycin lactobionate) is supplied as a sterile, lyophilized powder as follows:

List	Container	Concentration	Quantity
6476	Single-dose ADD-Vantage Vial	500 mg	Package of 10
6478	Single-dose ADD-Vantage Vial	1 g	Package of 10

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

Covered by one or more of the following U.S. patents: 4,614,515; 4,614,267.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard: *Performance Standards for Antimicrobial Disk Susceptibility Tests*, 3rd Edition, Vol. 4(16):M2-A3, Villanova, PA, December 1984.
2. Ericson, H.M., Sherris, J.C., Antibiotic Sensitivity Testing Report of an International Collaborative Study, *Acta Pathologica et Microbiologica Scandinavica* Section B Suppl. 217:1-90, 1971.
3. Committee on Rheumatic Fever and Infective Endocarditis of the Council on Cardiovascular Disease of the Young: Prevention of Rheumatic Fever, *Circulation* 70(6):1118A-1122A, December 1984.
4. Committee on Rheumatic Fever and Infective Endocarditis of the Council on Cardiovascular Disease of the Young: Prevention of Bacterial Endocarditis, *Circulation* 70(6):1123A-1127A, December 1984.

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