PRODUCT MONOGRAPH

CLINDAMYCIN INJECTION, USP

300, 600, 900 and 9,000 mg Clindamycin

Fliptop vials and ADD-Vantage* vials

Antibiotic

* TM

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#059114

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Clindamycin exerts its antibacterial activity by binding to the 50 S ribosomal subunit of susceptible bacteria, causing a reduction in the rate of synthesis of nucleic acid, and cessation of protein synthesis. It is primarily bacteriostatic, but may be bactericidal at high concentrations.

Following parenteral administration, biologically inactive clindamycin phosphate is rapidly hydrolyzed in plasma to active clindamycin.

By the end of short-term intravenous infusion, peak serum levels of active clindamycin are reached. Biologically inactive clindamycin phosphate disappears rapidly from the serum; the average disappearance half-life is 6 minutes; however, the serum disappearance half-life of active clindamycin is about 3 hours in adults and 2 1/2 hours in children.

After intramuscular injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in children.

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations for most indicated organisms by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in children, or by continuous intravenous infusion. An equilibrium state is reached by the third dose.

Clindamycin is widely and rapidly distributed to many body tissues and fluids, including saliva, ascites fluids, pleural fluids, synovial fluid, bone and bile. High concentrations are found in bone, bile, synovial fluid and urine. No significant levels of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges. Clindamycin readily crosses the placenta and is distributed into breast milk.

At a concentration of 1 μg/mL, clindamycin is approximately 93% bound to serum proteins.

The disappearance half-life of clindamycin is increased slightly (3 to 5 hours in adults) in patients with markedly reduced renal or hepatic function. Serum concentrations of the drug are not appreciably affected by hemodialysis, peritoneal dialysis, or prolonged administration in patients with normal renal function. Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease. (SEE PRECAUTIONS: Use in patients with special conditions)

Clindamycin is partially metabolized to bioactive and inactive metabolites. The major bioactive metabolites are clindamycin sulfoxide and N-demethylclindamycin which are excreted in the urine, bile and feces. Within 24 hours, approximately 10% of a total dose is eliminated in the urine and 3.6% in the feces as active drug and metabolites. The remainder is excreted as inactive metabolites.

INDICATIONS AND CLINICAL USES

CLINDAMYCIN INJECTION is indicated for the treatment of infection where the oral route is not indicated or feasible.

CLINDAMYCIN INJECTION is indicated in the treatment of serious infections due to sensitive anaerobic bacteria, such as Bacteroides species, Peptostreptococcus, anaerobic streptococci, Clostridium species and microaerophilic streptococci.

CLINDAMYCIN INJECTION is also indicated in the treatment of serious infections due to sensitive gram-positive organisms (staphylococci, including penicillinase-producing staphylococci, streptococci and pneumococci). However, in these infections the use of clindamycin should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate.

CLINDAMYCIN INJECTION may be used for the treatment of **serious infections** caused by susceptible strains of the designated microorganisms in the diseases listed below:

Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, *Streptococcus pneumoniae*, other streptococci (except *Enterococcus faecalis*), and *Staphylococcus aureus*.

Skin and skin structure infections caused by *Streptococcus pyogenes*, *Staphylococcus aureus* and anaerobes.

Gynecological infections including endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis, and postsurgical vaginal cuff infections caused by susceptible anaerobes.

Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.

Septicemia caused by *Staphylococcus aureus*, streptococci (except *Enterococcus faecalis*), and susceptible anaerobes.

Bone and joint infections including acute hematogenous osteomyelitis caused by *Staphylococcus aureus* and as adjunctive therapy in the surgical treatment of chronic bone and joint infections due to susceptible organisms.

Clindamycin is not indicated in the treatment of meningitis since it penetrates poorly into cerebrospinal fluid (CSF), even in the presence of inflamed meninges.

Indicated surgical procedures and drainage should be performed in conjunction with antibiotic therapy.

CONTRAINDICATIONS

CLINDAMYCIN INJECTION is contraindicated in patients previously found to be hypersensitive to clindamycin phosphate, the parent compound-clindamycin, or clindamycin palmitate. Patients hypersensitive to lincomycin (and possibly doxorubicin) may also be hypersensitive to clindamycin.

WARNINGS

Because of the risk of antibiotic-associated pseudomembranous colitis, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives. Clindamycin should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections.

Some cases of severe and persistent diarrhea have been reported during or after therapy with clindamycin. This diarrhea has been occasionally associated with blood and mucus in the stools and has at times resulted in acute colitis. When endoscopy has been performed, some of these cases have shown pseudomembrane formation.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin and may range from mild to life-threatening. Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

If clinically important or persistent diarrhea occurs during therapy, clindamycin therapy should be discontinued or, if necessary, continued only with close observation of the patient. Significant diarrhea occurring up to several weeks post therapy should be managed as if antibiotic-associated.

If colitis is suspected, endoscopy is recommended. Mild cases showing minimal mucosal changes may respond to simple drug discontinuance. Moderate to severe cases, including those showing ulceration or pseudomembrane formation, should be managed with fluid, electrolyte and protein supplementation as indicated. Corticosteroid retention enemas and systemic corticosteroids may be of help in persistent cases. Anticholinergics and antiperisaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen the condition. Other causes of colitis should be considered.

If colitis is moderate to severe or is not relieved by discontinuance of clindamycin, appropriate anti-infective therapy should be instituted.

Studies indicate a toxin(s) produced by Clostridia (especially *Clostridium difficile*) may be a principal cause of antibiotic-associated colitis. There are indications that the toxigenic Clostridium is usually sensitive *in vitro* to vancomycin. The administration of 125 mg to 500 mg of vancomycin orally 4 times a day for 5 to 10 or more days, resulted in a rapid disappearance of the toxin from faecal samples and a coincidental recovery from the diarrhea.

Cholestyramine and colestipol resins have been shown to bind clostridia-produced toxin(s) *in vitro*; however, the resins have also been shown to bind vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

Diarrhea, colitis and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin. A relatively prolonged period of continuing observation is therefore recommended.

Serious anaphylactoid reactions require immediate emergency treatment.

Benzyl alcohol toxicity

Clindamycin Injection contains benzyl alcohol (9.45 mg/mL) as a preservative. Benzyl alcohol in large doses (100 to 400 mg/kg daily) has been associated with toxicity i.e. "Gasping syndrome" in newborns, especially premature infants. The clinical syndrome is characterized by gasping respiration, hypotension, CNS depression, metabolic acidosis and renal failure which may progress to seizure, intracranial hemorrhage and death.

THEREFORE, CLINDAMYCIN INJECTION SHOULD BE USED CAUTIOUSLY IN NEWBORNS (INFANTS BELOW 30 DAYS OF AGE) PARTICULARLY IN THOSE ALSO RECEIVING OTHER BENZYL ALCOHOL-CONTAINING MEDICATION.

The attending physician must weigh the potential benefits against the possible risk. (See PRECAUTIONS: Use in newborns and infants)

PRECAUTIONS

General

CLINDAMYCIN INJECTION should be used with caution in atopic individuals.

Appropriate culture and susceptibility studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

CLINDAMYCIN INJECTION in Fliptop Vials must be further diluted prior to intravenous administration. The Injection should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes.

CLINDAMYCIN INJECTION, in the ADD-Vantage* vials is intended for intravenous use only after further dilution with appropriate volume of ADD-Vantage* Flexible Diluent Containers. (See DOSAGE AND ADMINISTRATION: Instructions for use)

The use of clindamycin may result in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfections occur, appropriate measures should be taken.

If a hypersensitivity reaction occurs during clindamycin therapy, the drug should be discontinued and appropriate therapy instituted as necessary. (See ADVERSE REACTIONS: Hypersensitivity Reactions)

During prolonged clindamycin therapy, liver and kidney function tests and blood cell counts should be performed periodically.

Use in elderly

Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Use in newborns and infants

When CLINDAMYCIN INJECTION is administered to newborns and infants, appropriate monitoring of organ system functions is desirable (See WARNINGS: benzyl alcohol toxicity).

Use in pregnancy

The safe use of clindamycin in pregnancy has not been established. Clindamycin crosses the placenta and may be concentrated in the fetal liver.

Use in nursing mothers

Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 μg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for serious adverse reactions from clindamycin in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Use in patients with special conditions

CLINDAMYCIN INJECTION may be used in anuretic patients. Since the serum half-life of clindamycin phosphate in patients with impaired hepatic function is greater than that found in normal patients, the dose of the drug should, therefore be appropriately decreased.

Hemodialysis and peritoneal dialysis are not effective means of removing the compound from the blood. Periodic determination of serum levels of clindamycin should be performed in patients with severe hepatic and renal insufficiency.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Clindamycin should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Drug interactions:

- Erythromycins: Antagonism of bactericidal activity has been demonstrated between clindamycin and erythromycin *in vitro*.

- In vitro experiments have demonstrated that these agents may displace clindamycin from or prevent its binding to 50S subunits of bacterial ribosomes, thus antagonizing the effects of clindamycin. Because of possible clinical significance, these two drugs should not be administered concurrently.

- Neuromuscular blocking agents: Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents concurrently.

ADVERSE REACTIONS

The following reactions have been reported with the use of clindamycin.

Gastrointestinal: Abdominal pain, nausea, vomiting and diarrhea (See WARNINGS). An unpleasant or metallic taste occasionally has been reported after intravenous administration of high doses of clindamycin phosphate.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbiliform-like skin rashes are the most frequently reported adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, oxygen, corticosteroids, antihistamines) should be available for emergency treatment of serious anaphylactoid reactions.

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Renal: Although no direct relationship of clindamycin to renal damage has been established, renal dysfunction as evidenced by azotemia, oliguria, and/or proteinuria has been observed in rare instances.

Hematopoietic: Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Musculoskeletal: Rare instances of polyarthritis have been reported.

Cardiovascular: Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration (See DOSAGE AND ADMINISTRATION).

Local reactions: Pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

Clinical and laboratory findings: Transient increases in serum bilirubin, alkaline phosphatase and AST (SGOT) concentrations have occurred in some patients. The relationship of liver function abnormality to clindamycin is not known.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No cases of overdosage have been reported. No specific antidote is known. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

DOSAGE AND ADMINISTRATION

CLINDAMYCIN INJECTION in Fliptop vials is intended for both intramuscular and intravenous (after dilution) administration; the ADD-Vantage* vials are for intravenous (after dilution) administration only. (See INSTRUCTIONS FOR USE)

Dosage is expressed in terms of clindamycin and depends on the severity of the infection and the susceptibility of the infecting organism.

In the treatment of serious anaerobic infections, parenteral clindamycin is usually used initially and oral clindamycin may be substituted when the condition of the patient warrants.

The duration of clindamycin therapy depends on the type and severity of infection. In infections caused by group A ß-hemolytic streptococci, clindamycin therapy should be continued for at least 10 days.

Adults:

Intramuscular Injection:

- Serious Infections: 600 mg/day in 2 equal doses.
- Moderately severe infections: 600 to 1200 mg/day in 2 or 3 equal doses.
- Severe infections: 1200 to 2400 mg/day in 2, 3 or 4 equal doses.

Note: Intramuscular injections of more than 600 mg into a single site are not recommended.

Intravenous administration:

CLINDAMYCIN INJECTION **must be diluted** prior to I.V. administration to a concentration of 600 mg in 50 ml of diluent (12 mg/mL) or less, and infused in not less than 10 minutes (maximum 30 mg per min) (see Table 1). Administration of more than 1200 mg in a single one hour infusion is not recommended. **The Injection should not be injected intravenously undiluted as a bolus.**

- Moderately severe infections: 900 to 1800 mg/day by continuous drip or in 2 or 3 equal doses, each infused over 20 minutes or longer.

- Severe infections: 1800 to 2700 mg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer.

- Life-threatening infections: 2700 to 4800 mg/day by continuous drip or in 3 or 4 equal doses each infused over 20 minutes or longer may be given

Table 1
Dilution and Infusion Rates

Total Dose (mg)	Diluent (mL)	Concentration Clindamycin mg/mL	Time (minutes)
300	50	6	10
600	50	12	20
900	100	9	30
1200	100	12	40

Alternatively, the drug may be administered in the form of a single rapid infusion of the first dose followed by continuous I.V. infusion as follows:

Table 2
Recommended Infusion Rate

To maintain serum clindamycin levels	Rapid infusion rate	Maintenance infusion rate
>4 μg/mL	10 mg/min. for 30 min.	0.75 mg/min.
>5 μg/mL	15 mg/min. for 30 min.	1.00 mg/min.
>6 μg/mL	20 mg/min. for 30 min.	1.25 mg/min.

Children: (Over one month of age)

Intramuscular Injection:

. Serious infections: 10 to 15 mg/kg/day in 2, 3 or 4 equal doses.

. Moderately severe infections: 15 to 20 mg/kg/day in 3 or 4 equal doses.

. Severe infections: 20 to 30 mg/kg/day in 3 or 4 equal doses.

Intravenous Administration:

. Moderately severe infections: 15 to 25 mg/kg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer.

. Severe infections: 25-40 mg/kg/day in 3 or 4 equal doses. It is recommended that children be given no less than 300 mg/day, regardless of body weight.

As an alternative to dosing on a body weight basis, children may be dosed on the basis of square meters body surface: 350 mg/m^2/day for serious infections and 450 mg/m^2/day for more severe infections.

PHARMACEUTICAL INFORMATION

Drug substance

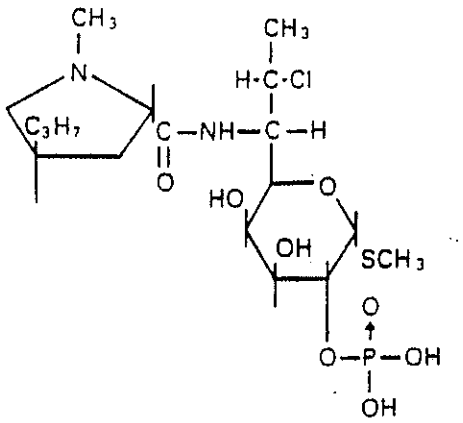
Proper Name: Clindamycin Phosphate, USP

Chemical Names:

L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6, 7,8-trideoxy-6 -[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, 2-(dihydrogen phosphate), (2S-trans)-

or 7(s)-chloro-7-deoxylincomycin 2-phosphate.

Structural formula:



Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$

Molecular Weight: 504.96

Description:

Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

Clindamycin phosphate is a water soluble ester of clindamycin and phosphoric acid. It is a white to off-white hygroscopic crystalline powder. It is slightly soluble in ethanol, practically insoluble in chloroform and in ether. The pH of clindaymycin phosphate is between 3.5 and 4.5 in a 1% w/v solution. The pKa is 7.6.

Composition:

Clindamycin Injection, USP is a sterile nonpyrogenic solution of clindamycin (as phosphate). Each mL contains clindamycin phosphate equivalent to clindamycin 150 mg; disodium edetate 0.5 mg (as a stabilizer) and benzyl alcohol 9.45 mg (as preservative). It may contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH is 6.4 (5.5 to 7.0).

Stability and Storage Recommendations:

Store at 15°-25°C. Protect from freezing and excessive heat.

INSTRUCTIONS FOR USE

Fliptop Vials

Clindamycin Injection in Fliptop vials must be diluted prior to I.V. .administration. The usual infusion dilutions are as follows:

Dilution Table

Vial Size (mL)	Total Dose (mg)	Diluent (mL)	Concentration Clindamycin (mg/mL)
2	300	50	6
4	600	50	12
6	900	100	9

Compatibility

Clindamycin Injection was found to be physically compatible and demonstrated no significant change in pH or antimicrobial potency over a period of 24 hours in the following infusion solutions:

- Sodium Chloride injection
- Dextrose 5% injection
- Dextrose 5% in Sodium Chloride injection
- Dextrose 5% in Ringer's Solution
- Dextrose 5% in 0.45% Sodium chloride injection plus 40 mmol (40 mEq) potassium chloride.
- Dextrose 2.5% in Lactated Ringer's Solution (Hartmann's Solution)

Clindamycin phosphate has been shown to be compatible with gentamicin sulfate, tobramycin sulfate and amikacin sulfate.

ADD-Vantage* Vials

Clindamycin Injection in ADD-Vantage* vials is designed to be used exclusively with ADD-Vantage* Flexible Diluent Containers of 5% Dextrose Injection, USP and 0.9% Sodium Chloride Injection, USP as below.

Dilution Table

Vial Size (mL)	Total Dose (mg)	Diluent to use (mL)	Concentration Clindaymycin (mg/mL)
2	300	50	6
4	600	50	12
6	900	100	9

The reconstituted solutions are stable for 24 hours at room temperature, or up to 72 hours under refrigeration (2° to 8°C); unused reconstituted portion must be discarded.

Incompatibility

Clindamycin Injection demonstrated no incompatibility for 24 hours at room temperature in I.V. solutions containing sodium chloride, glucose, calcium or potassium, and solutions containing Vitamin B complex in concentrations used clinically.

The following drugs are physically incompatible with clindamycin phosphate: ampicillin, phenytoin sodium, barbiturates, aminophylline, calcium gluconate and magnesium sulfate.

Instructions of use of ADD-Vantage*

To Use Vial in ADD-Vantage® Flexible Diluent Container

INSTRUCTIONS FOR USE
These instructions for use should be made available to the individuals who perform the reconstitution steps.

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 Fig. 1)**. Then pull straight up to remove the cap **(see Fig. 2)**.
   NOTE: Once the breakaway cap has been removed, 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 Fig. 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 Fig. 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 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.

Fig. 3

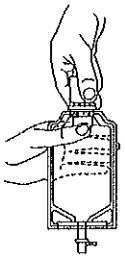


Fig. 4

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 Fig. 5)**.
3. **Pull the inner cap from the drug vial (see Fig. 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.
5. Look through the bottom of the vial to verify that the stopper has been removed and complete mixing has occurred **(see Fig. 7)**.

If the rubber stopper is not removed from the vial and medication is not released on the first attempt, the inner cap may be manipulated back into the rubber stopper without removing the drug vial from the diluent container. Repeat steps 3 through 5.

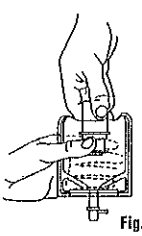


Fig. 5

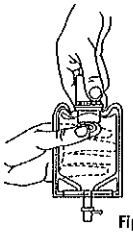


Fig. 6

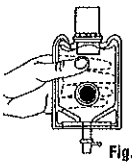


Fig. 7

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 container in series connections.

For both Fliptop Vials and ADD-Vantage* Vials

Clindamycin Injection in Fliptop vials and ADD-Vantage* vials are intended for single use only. Unused portion must be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless solution is clear.

AVAILABILITY OF DOSAGE FORMS

Clindamycin Injection, USP is supplied in single dose and multiple dose (Pharmacy Bulk Pack) Fliptop vials and ADD-Vantage* vials as follows:

Fliptop Vials: For I.M. or I.V. Use

- 150 mg/mL** in 2mL (300 mg/2mL), List No. L748
- 150 mg/mL in 4mL (600 mg/4mL), List No. L748
- 150 mg/mL in 6mL (900 mg/6mL), List No. L748
- 150 mg/mL in 60 mL (9,000 mg/60mL), List No. L748

These presentations MUST BE DILUTED PRIOR TO INTRAVENOUS USE

ADD-Vantage* Vials: For I.V. use only after dilution with ADD-Vantage* Flexible Diluent Containers.

- 150 mg/mL** in 2mL (300 mg/2mL), List No. 4053
- 150 mg/mL in 4mL (600 mg/4mL), List No. 4054
- 150 mg/mL in 6mL (900 mg/6mL), List No. 4055

** equivalent in Clindamycin

MICROBIOLOGY

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

Aerobic gram positive cocci, including:
Staphylococcus aureus
Staphylococcus epidermidis
(penicillinase and nonpenicillinase producing strains). When tested by *in vitro* methods some staphylococcal strains originally resistant to erythromycin rapidly develop resistance to clindamycin.
Streptococci (except Enterococcus faecalis)
Pneumococci

Anaerobic gram negative bacilli, including:
Bacteroides species (including Bacteroides fragilis group and Bacteroides melaninogenicus group)
Fusobacterium species

Anaerobic gram positive nonsporeforming bacilli, including:
Propionibacterium
Eubacterium
Actinomyces species

Anaerobic and microaerophilic gram positive cocci, including:
Peptococcus species
Peptostreptococcus species
Microaerophilic streptococci

Clostridia: Clostridia are more resistant than most anerobes to clindamycin. Most *Clostridium perfringens* are susceptible, but other species, eg. *Clostridium sporogenes* and *Clostridium tertium* are frequently resistant to clindamycin. Susceptibility testing should be performed.

The *in vitro* activity of clindamycin against clinical isolates of gram positive and gram negative aerobic and anaerobic bacteria is shown in Table 3. Table 4 provides the ranges of MICs and the MICs required to inhibit 50% (MIC_{50}) and 90% (MIC_{90}) of bacteria.

Table 3
In Vitro Sensitivities of Aerobic, Facultative Anaerobic, and Anaerobic Bacteria to Clindamycin

Organism	USUAL MIC (mg/L) Clindamycin
Gram-positive	
Staphylococcus aureus	0.04-0.4
Staphylococcus epidermidis	0.1-0.2
Streptococcus pneumoniae	0.01-0.06
Streptococcus pyogenes	0.02-0.02
Streptococcus viridans	0.01-0.06
Streptococcus faecalis	12.5->100
Corynebacterium diphtheriae	≤0.2
Nocardia spp.	0.78-25
Gram-negative	
Neisseria gonorrhoeae	0.01-6.3
Neisseria meningitidis	5-25
Hemophilus influenzae	0.4-50
Escherichia, Klebsiella, Enterobacter, Serratia, Proteus, Pseudomonas spp.	25->100
Salmonella spp.	12-25
Shigella spp.	25
Anaerobic, gram-negative bacilli	
Bacteroides fragilis group*	≥0.1-3.1
Bacteroides melaninogenicus	≥0.1-0.2
Fusobacterium spp.	≥0.1-1.6
Anaerobic, gram-positive bacilli	
Actinomyces spp.	0.03-0.25
Bifidobacterium spp.	≥0.01
Eubacterium spp.	≥0.1-0.8
Propionibacterium spp.	≥0.1-0.2
Anaerobic, spore-forming bacilli	
Clostridium perfringens	≥0.1-3.1
Clostridium spp.	≥0.1-3.1
Anaerobic cocci	
Peptococcus spp.	≥0.1-3.1
Peptostreptococcus spp.	≥0.1-0.8
Veillonella spp.	≥0.1

* B. fragilis group includes B. fragilis, B. thetaiotao micron, B. distasonis, B. vulgatus, and B. ovatus.

TABLE 4

IN VITRO SUSCEPTIBILITY OF DIFFERENT ANAEROBES TO CLINDAMYCIN

Microorganisms	Number of Strains	MIC (mg/L)		
		Range	50%	90%
Bacteroids fragilis group	304	≤0.12->8	0.5	4
Non-Bacteroids fragilis group*	142	≤0.12-8	≤0.12	1
Fusobacterium species	50	≤0.12-8	0.5	4
All ß-lactamase-positive isolates	496	≤0.12-8	0.25	4
All ß-lactamase-negative isolates	44	≤0.12-2	≤0.12	0.5

* includes non-ß.fragilis group Bacteroides species and Prevotella and Porphyromonas species.

In vitro, clindamycin concentrations of 0.04 - 0.4 μg/mL inhibits most susceptible strains of staphylococci, streptococci, pneumococci, *Corynebacterium diphtheria* and Actinomyces. The minimum inhibitory concentration (MIC) of clindamycin for most susceptible anerobic and microaerophilic bacteria is 0.1 - 4 μg/mL.

Susceptibility Testing

Susceptibility testing may be done either by tube or agar dilution methods for both anaerobic and aerobic bacteria. A bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) for clindamycin is not more than 1.6 μg/mL. Organisms are considered moderately susceptible if the MIC is greater than 1.6 μg/mL and less than 4.8 μg/mL. Organisms are considered resistant if the MIC is greater than 4.8 μg/mL.

The range of MICs for control strains are given in Table 5.

Table 5

Strain		MIC (μg/mL)
S. aureus	ATCC 29213	0.06 - 0.25
S. faecalis	ATCC 29212	4.0 - 16

National Committee for Clinical Lab Standards. Methods for Antimicrobial Susceptibility testing of Anaerobic Bacteria. Second Edition, Tentative Standard. NCCLS publication M11-T2, Villanova, PA;NCCLS 1988

Note: Susceptibility testing of anerobic bacteria does not necessarily correlate with clinical efficacy. The Kirby-Bauer Disk diffusion method and its interpretive standards are not recommended for anaerobes.

The standard single disk method of susceptibility testing using a disc containing 2 μg of clindamycin should be interpreted according to the following criteria:

Table 6

Susceptibility Category	Zone Diameter (mm)
Susceptible	≥17
Intermediate	15-16
Resistant	≤14

The 2 μg clindamycin disk should give a zone diameter of between 24 and 30 mm for *S. aureus* ATCC 25923.

Development of Resistance

Staphylococcal resistance to clindamycin has been induced *in vitro* and has been shown to be acquired in a stepwise manner. Complete cross-resistance occurs between clindamycin and lincomycin, and there is evidence of partial cross-resistance between clindamycin and erythromycin.

In vitro, bacteria resistant to erythromycin and susceptible to clindamycin may exhibit a dissociated type of resistance to clindamycin during susceptibility testing if erythromycin is also present. The phenomenon may be the result of competition between erythromycin and clindamycin for the ribosomal binding site.

PHARMACOLOGY

Serum Concentrations via the I.V./I.M. routes in Adults

Clindamycin phosphate is absorbed as the inactive ester and is rapidly hydrolyzed in the blood to the active base. After multiple dose intramuscular administration of clindamycin phosphate, mean peak serum levels of clindamycin are reached in 3 hours and are about 6 μg/mL after a 300 mg dose and 9 μg/mL after a 600 mg dose.

Serum level curves may be constructed from I.V. peak serum levels as given in Table 7 by application of disappearance half-lives.

Table 7
Average Peak Serum Concentrations After Dosing with Clindamycin Phosphate

Dosage Regimen	Clindamycin+ (mg/L)	Clindamycin Phosphate (mg/L)
Healthy Adult Males (Post equilibrium)		
300 mg I.V. in 10 min. q8h	7	15
600 mg I.V. in 20 min. q8h	10	23
900 mg I.V. in 30 min. q12h	11	29
1200 mg I.V. in 45 min. q12H	14	49
300 mg I.M. q8h	6	3
600 mg I.M. q12h*	9	3
Children (first dose)*		
5-7 mg/kg I.V. in 1 hr	10	
3-5 mg/kg I.M.	4	
5-7 mg/kg I.M.	8	

* Data in this group from patients being treated for infection

\+ Serum assays for active clindamycin require an inhibitor to prevent *in vitro* hydrolysis of clindamycin phosphate.

In adult healthy volunteers, immediately following multiple intravenous infusions of 300, 600, 900, or 1200 mg of clindamycin phosphate, serum levels of clindamycin base are 7, 10, 11, and 14 μg/mL, respectively.

There was no evidence of drug accumulation or enzyme induction in adult volunteers receiving 300 mg every 8 hours for 14 days.

Serum Levels via I.V./I.M. routes in Infants and Neonates

The pharmacokinetics of intravenously administered clindamycin phosphate was studied in 40 children < 1 year of age. Mean peak serum clindamycin concentrations were 10.92 μg/mL in premature infants <4 weeks of age, 10.45 μg/mL in term infants >4 weeks, and 12.69 μg/mL in term infants <4 weeks of age.

In children with infections who received 5-7 mg/kg clindamycin phosphate by single I.V. infusion over 1 hour or by I.M. injection, serum concentrations of clindamycin were 10 or 8 μg/mL, respectively.

Distribution

Table 8 provides tissue and body fluid levels of clindamycin base following administration of clindamycin phosphate. Clindamycin does not cross the blood-brain barrier even in the presence of inflamed meninges.

Table 8
Clindamycin concentrations in body tissues and fluids

Specimen	Dosage Regimen Clindamycin Phosphate	Tissue or fluid level
Bone	300 mg I.M. q8h	6.4 μg/g
Bone	600 mg I.M. q8h	1.44 μg/g
Bone	600 mg I.V. q8h	0.75 μg/g
Bone marrow	600 mg I.M. q8h	10.83 μg/g
Bile	300 mg I.V. q6h	2.70 μg/mL
Synovial fluid	300 mg I.M. q8h	4.87 μg/mL
Pleural fluid	600 mg I.V. q8h	3.9 μg/mL

Elimination

The serum half-life of clindamycin is 2-3 hours in adults and children with normal renal function. The serum half-life is increased slightly in patients with markedly reduced renal or hepatic function. The mean half-life was 3.0 hours in patients with impaired renal function and 4.5 hours in those with impaired liver function.

In neonates, the serum half-life depends on gestational and chronologic age and body weight. The serum half-life of clindamycin reportedly averages 8.7 and 3.6 hours in premature and full-term neonates, respectively, and about 3 hours in infants 4 weeks to 1 year of age; serum half-life was longer in infants weighing less than 3.5 kg than in heavier infants.

TOXICOLOGY

Acute

The results of acute toxicity studies of clindamycin administered by a variety of routes in mice and rats, are presented in Table 9.

Table 9
LD_{50} of Clindamycin

Species	Route	LD_{50} (mg/kg)
Adult Mouse	I.P.	1145
Adult Mouse	I.V.	855
Adult Rat	P.O.	1832
Adult Rat	S.C.	>2000
Newborn Rat	S.C.	179

Other Studies

Rabbits

Intramuscular irritation study in rabbits

Single injections of clindamycin phosphate in concentrations of 50, 100, 200 and 300 mg in 1 mL cisotonic saline were injected into the loin muscles of New Zealand white rabbits. The injected sites were graded according to degree of hemorrhage, degeneration and necrosis at three and seven days after injection, and compared to controls. Slight to moderate irritation was noted after these injections, but all concentrations were about equally well tolerated.

Rats

Six day subcutaneous tolerance study in the rat

1 mL of a 300 mg/mL solution of clindamycin phosphate was injected into the interscapular subcutaneous tissue of 10 male Sprague-Dawley rats daily for six days (the equivalent of 120 mg/kg/day). Local evidence of multiple epidermal breakdown with scab formation over the injection site was present in most rats. No systemic evidence of drug effect was detected at necropsy. Organ weights were not significantly different from control animals and likewise no significant deviations of hematologic data were noted among treated animals.

One month subacute subcutaneous toxicity in the rat

Clindamycin phosphate at dose levels of 30, 60 and 90 mg/kg (using 300 mg/mL solution) was injected under the back skin of groups of 10 Sprague-Dawley rats daily for one month. No drug-related systemic effects were observed. Local inflammatorychanges were seen at all three dose levels. Injections of the 60 and 90 mg/kg doses caused more extensive inflammatory changes and were more frequently accompanied by focal necrosis of the subcutaneous tissues and overlying epidermis.

Dogs

Six day intramuscular tolerance study in dogs

Clindamycin phosphate at dose levels equivalent to 60 mg/kg/day was injected into the thigh muscles of three beagles daily for six days, 1 mL into each thigh. These doses were well tolerated by the dogs.

Serum transaminase values were elevated terminally with SGOT values increasing in advance of SGPT values, suggesting that the source of these changes was the injected muscles.

No other evidence of treatment-related changes was noted. Gross pathological changes were confined to the injection sites. The subcutaneous connective tissue showed signs of slight hemorrhage and edema.

One month subacute intramuscular toxicity in the dog

Clindamycin phosphate at dose levels of 30, 60 and 90 mg/kg (using 300 mg/mL solution) was injected intramuscularly into three groups of three dogs daily for 32 days. Clindamycin phosphate was found to be mildly to moderately irritating as evidenced by a dose related progressive scarring of the muscle bundle. Elevations of SGOT and SGPT were noted in all treated dogs. Other blood evaluations and liver function tests were in the normal range. A slight dose-related increase in liver weight was observed, but no morphologic evidence of drug effect on the liver was obtained.

Lymphocytic infiltrations were observed in the thyroid glands of 3 dogs (control, 30 and 90 mg/kg groups). In another dog receiving 60 mg/kg, both lobes of the thyroid gland showed an embryonal-type epithelial hyperplasia. However, this finding was not considered to be drug-related.

One month subacute intravenous toxicity in the dog

Clindamycin phosphate at a dose of 60 and 120 mg/kg was injected intravenously in two groups of four dogs, 6 days a week for one month. All injections were given into the cephalic veins and were administered slowly over a period of 10 minutes. No drug-related effects were observed in any of the animals during or after the intravenous administrations. In particular, there was no evidence of drug-induced hemolysis or drug-related changes in the cephalic veins on both gross and microscopic examinations.

REPRODUCTION AND TERATOLOGY

Teratology study in the rat

Clindamycin phosphate was found to be not teratogenic when given subcutaneously to pregnant Sprague Dawley rats from gestation day 6 through 15 at levels of 100 and 180 mg/kg/day. Neither of the doses tested had any detrimental effect on reproductive performance.

Teratology study in the mouse

Clindamycin phosphate was administered to ICR and CFL strains of mice by subcutaneous injection of 100 and 180 mg/kg/day on gestation days 6 through 15. A low incidence of cleft palate occurred in the ICR strain in the initial experiment and as a result the study was repeated twice with no abnormalities noted. No cases of cleft palate were observed in the second strain of mice. The occurrence of cleft palate in the ICR strain of mice was not considered to be drug-related.

One generation rat reproduction study

Clindamycin phosphate was administered orally in the diet to rats at doses of 100 and 300 mg/kg/day for one generation. No biologically significant effect on the reproductive parameters studied was noted. The weights of pups from treated females were reduced slightly at birth and weaning but post-natal survival rate was not adversely affected. None of the pups exhibited significant morphologic abnormalities.

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