CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-027

APPROVED DRAFT LABELING

50634

Cleocin Phosphate®

Sterile Solution

Pharmacia &Upjohn

clindamycin phosphate injection, USP and clindamycin phosphate injection in 5% dextrose

Sterile Solution is for intramuscular and intravenous use

CLEOCIN PHOSPHATE in the ADD-Vantage™ Vial is For Intravenous Use Only

JUN 8 1998

Cleocin Phosphate clindamycin phosphate sterile solution and clindamycin phosphate IV solution

0810020033

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WARNING

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

Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS AND USAGE section. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

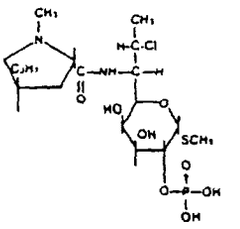
DESCRIPTION

CLEOCIN PHOSPHATE Sterile Solution in vials contains clindamycin phosphate, a water soluble ester of clindamycin and phosphoric acid. Each mL contains the equivalent of 150 mg clindamycin, 0.5 mg disodium edetate and 9.45 mg benzyl alcohol added as preservative in each mL. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

Cleocin Phosphate

brand of clindamycin phosphate injectio
clindamycin phosphate injection in 5% d

The chemical name of clindamycin phosp
pyranoside, methyl 7-chloro-6,7,8-trideoxy-6-
carbonyl] amino]-1-thio-, 2-(dihydrogen phospn
The molecular formula is $C_{18}H_{34}ClN_2O_8PS$ an
The structural formula is represented below:



mg/mL. The pH has been adjusted with sodium
The plastic container is fabricated from a sp
2501. Solutions in contact with the plastic c
chemical components in very small amounts
ability of the plastic has been confirmed in te
biological tests for plastic containers, as well

CLINICAL PHARMACOLOGY

Biologically inactive clindamycin phosp
clindamycin.

By the end of short-term intravenous infus
damycin are reached. Biologically inactive
rapidly from the serum; the average eliminati
serum elimination half-life of active clindamyc
hours in children.

After intramuscular injection of clindamycin
damycin are reached within 3 hours in adult
curves may be constructed from IV peak seru
cation of elimination half-lives listed above.

Serum levels of clindamycin can be ma
inhibitory concentrations for most indicated
damycin phosphate every 8 to 12 hours in ad
or by continuous intravenous infusion. An eq
dose.

The elimination half-life of clindamycin
markedly reduced renal or hepatic function
are not effective in removing clindamycin fro
not be modified in the presence of mild or mo

No significant levels of clindamycin are att
the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunte
(18-39 years) indicate that age alone does
(clearance, elimination half-life, volume of
concentration-time curve) after IV administ
oral administration of clindamycin hydrochlo
approximately 4.0 hours (range 3.4–5.1 h)
(range 2.1–4.2 h) in younger adults. The ex
ferent between age groups and no dosage
with normal hepatic function and normal (age

Serum assays for active clindamycin requir
sis of clindamycin phosphate.

Table 1. Average Peak and Trough S
Clindamycin After Dosing w

Dosage Regimen	
Healthy Adult Males (Post equilibrium)	
600 mg IV in 30 min q6h	
600 mg IV in 30 min q8h	
900 mg IV in 30 min q8h	
600 mg IM q12h*	
Children (first dose)*	
5–7 mg/kg IV in 1 hour	
5–7 mg/kg IM	
3–5 mg/kg IM	

*Data in this group from patients being tre

Pharmacia & Upjohn

...damycin

...ravenous Use

...Vial Is For

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...with nearly all antibac-
...in severity from mild
...consider this diagnosis in
...to the administration of
...with severe colitis which
...infections where less toxic
...in the INDICATIONS AND
...with nonbacterial infections
...Treatment with antibacterial
...and may permit overgrowth of
...by *Clostridium difficile* is one
...has been established.
...of pseudomembranous
...in moderate to severe
...with fluids and elec-
...with an antibacterial drug clin-
...have been observed to
...of therapy with clindamycin.

...contains clindamycin phosphate,
...acid. Each mL contains the
...edetate and 9.45 mg benzyl
...is a semisynthetic antibiotic
...hydroxyl group of the parent

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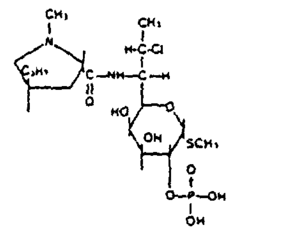
brand of clindamycin phosphate injection, USP and clindamycin phosphate injection in 5% dextrose

The chemical name of clindamycin phosphate is 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), (2*S*-*trans*)-.

The molecular formula is $C_{18}H_{34}ClN_2O_8PS$ and the molecular weight is 504.96.

The structural formula is represented below:



CLEOCIN PHOSPHATE in the ADD-Vantage Vial is intended for intravenous use only after further dilution with appropriate volume of ADD-Vantage diluent base solution.

CLEOCIN PHOSPHATE IV Solution in the Galaxy® plastic container for intravenous use is composed of clindamycin phosphate equivalent to 300, 600 and 900 mg of clindamycin premixed with 5% dextrose as a sterile solution. Disodium edetate has been added at a concentration of 0.04 mg/mL. The pH has been adjusted with sodium hydroxide and/or hydrochloric acid.

The plastic container is fabricated from a specially designed multilayer plastic, PL 2501. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. The suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Biologically inactive clindamycin phosphate is rapidly converted 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 elimination half-life is 6 minutes; however, the serum elimination half-life of active clindamycin is about 3 hours in adults and 2½ 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 level curves may be constructed from IV peak serum levels as given in Table 1 by application of elimination half-lives listed above.

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 to 12 hours in adults and every 6 to 8 hours in children, or by continuous intravenous infusion. An equilibrium state is reached by the third dose.

The elimination half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease.

No significant levels of clindamycin are attained in the cerebrospinal fluid even in the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunteers (61-79 years) and younger adults (18-39 years) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentration-time curve) after IV administration of clindamycin phosphate. After oral administration of clindamycin hydrochloride, elimination half-life is increased to approximately 4.0 hours (range 3.4–5.1 h) in the elderly compared to 3.2 hours (range 2.1–4.2 h) in younger adults. The extent of absorption, however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function[1].

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

Table 1. Average Peak and Trough Serum Concentrations of Active Clindamycin After Dosing with Clindamycin Phosphate

Dosage Regimen	Peak mcg/mL	Trough mcg/mL
Healthy Adult Males (Post equilibrium)		
600 mg IV in 30 min q6h	10.9	2.0
600 mg IV in 30 min q8h	10.8	1.1
900 mg IV in 30 min q8h	14.1	1.7
600 mg IM q12h*	9	
Children (first dose)*		
5–7 mg/kg IV in 1 hour	10	
5–7 mg/kg IM	8	
3–5 mg/kg IM	4	

*Data in this group from patients being treated for infection.

Cleocin Phosph...

brand of clindamycin phosph... clindamycin phosphate injec...

Microbiology: Although clindam... hydrolysis converts this compound... Clindamycin has been shown to... lowing organisms:

Aerobic gram positive cocci, inclu...
Staphylococcus aureus (peni...
Staphylococcus epidermidis strain... staph... mycin...
Streptococci (except *Enterococ...*
Pneumococci

Anaerobic gram negative bacilli, in...
Bacteroides species (including ... *melaninogenicus* group)
Fusobacterium species

Anaerobic gram positive nonspore...
Propionibacterium
Eubacterium
Actinomyces species

Anaerobic and microaerophilic gra...
Peptococcus species
Peptostreptococcus species
Microaerophilic streptococci

Clostridia: Clostridia are more res... Clostridium perfringens are susce... genes and Clostridium tertium are... testing should be done.

Cross resistance has been dem...
Antagonism has been demonstr...

***In vitro* Susceptibility Testing:**

Disk diffusion technique-Quanti... diameters give the most precise... procedure[2] has been recommen... clindamycin.

Reports from a laboratory usin... with a 2 mcg clindamycin disk ... criteria:

Susceptible organisms produce... tested organism is likely to resp...
Organisms of intermediate sus... that the tested organism would... infection is confined to tissues... levels are attained.
Resistant organisms produce zo... should be selected.
Standardized procedures requ... damycin disk should give a zon... ATCC 25923.

Dilution techniques—A bacter... minimum inhibitory concentrat... mcg/mL. Organisms are consid... than 1.6 mcg/mL and less than... ered resistant if the MIC is grea...

The range of MICs for the cont...
S. aureus ATCC 29213, 0.06...
E. faecalis ATCC 29212, 4.0-...

For anaerobic bacteria the mini... can be determined by agar dilutio... niques.[3] If MICs are not determ... mended for routine use. THE KIR... INTERPRETIVE STANDARDS AR...

INDICATIONS AND USAGE

CLEOCIN PHOSPHATE produc... tions caused by susceptible anae...

CLEOCIN PHOSPHATE produc... infections due to susceptible str... cocci. Its use should be reserved... whom, in the judgment of the phy... risk of antibiotic-associated pseu... ING box, before selecting clinda... the infection and the suitability of...

Bacteriologic studies should be... and their susceptibility to clindam...

Indicated surgical procedures ... therapy.

Cleocin Phosphate

brand of clindamycin phosphate injection, USP and clindamycin phosphate injection in 5% dextrose

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 (penicillinase and non-penicillinase producing strains). When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly develop resistance to clindamycin.

Staphylococcus epidermidis

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 anaerobes to clindamycin. Most *Clostridium perfringens* are susceptible, but other species, e.g., *Clostridium sporogenes* and *Clostridium tertium* are frequently resistant to clindamycin. Susceptibility testing should be done.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

***In vitro* Susceptibility Testing:**

Disk diffusion technique-Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure[2] has been recommended for use with disks to test susceptibility to clindamycin.

Reports from a laboratory using the standardized single-disk susceptibility test[1] with a 2 mcg clindamycin disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 17 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones of 15-16 mm, indicating that the tested organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Standardized procedures require the use of control organisms. The 2 mcg clindamycin disk should give a zone diameter between 24 and 30 mm for *S. aureus* ATCC 25923.

Dilution techniques—A bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) for clindamycin is not more than 1.6 mcg/mL. Organisms are considered moderately susceptible if the MIC is greater than 1.6 mcg/mL and less than or equal to 4.8 mcg/mL. Organisms are considered resistant if the MIC is greater than 4.8 mcg per mL.

The range of MICs for the control strains are as follows:

S. aureus ATCC 29213, 0.06—0.25 mcg/mL.

E. faecalis ATCC 29212, 4.0—16 mcg/mL.

For anaerobic bacteria the minimum inhibitory concentration (MIC) of clindamycin can be determined by agar dilution and broth dilution (including microdilution) techniques.[3] If MICs are not determined routinely, the disk broth method is recommended for routine use. THE KIRBY-BAUER DISK DIFFUSION METHOD AND ITS INTERPRETIVE STANDARDS ARE NOT RECOMMENDED FOR ANAEROBES.

INDICATIONS AND USAGE

CLEOCIN PHOSPHATE products are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

CLEOCIN PHOSPHATE products are also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of antibiotic-associated pseudomembranous colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

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

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

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brand of clindamycin phosphate injection, USP and clindamycin phosphate injection in 5% dextrose

CLEOCIN PHOSPHATE is indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, *Streptococcus pneumoniae*, other streptococci (except *E. 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 infection 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.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

WARNINGS

See WARNING box.

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

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants. (See PRECAUTIONS–Pediatric Use.)

Usage in Meningitis—Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General

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.

CLEOCIN PHOSPHATE products should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

CLEOCIN PHOSPHATE should be prescribed with caution in atopic individuals.

Certain infections may require incision and drainage or other indicated surgical procedures in addition to antibiotic therapy.

The use of CLEOCIN PHOSPHATE may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

CLEOCIN PHOSPHATE should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in the DOSAGE AND ADMINISTRATION section.

Clindamycin dosage modification may not be necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of clindamycin half-life has been found. However, it was postulated from studies that when given every eight hours, accumulation should rarely occur. Therefore, dosage modification in patients with liver disease may not be necessary. However, periodic liver enzyme determinations should be made when treating patients with severe liver disease.

Laboratory Tests

During prolonged therapy periodic liver and kidney function tests and blood counts should be performed.

Drug Interactions

Clindamycin has been shown to have neuromuscular blocking properties that may

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enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic effects

Pregnancy category B

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (2.1 and 1.1 times the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (0.9 and 0.5 times the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for adverse reactions due to clindamycin in neonates (see **Pediatric Use**), the decision to discontinue the drug should be made, taking into account the importance of the drug to the mother.

Pediatric Use

When CLEOCIN PHOSPHATE Sterile Solution is administered to the pediatric population (birth to 16 years) appropriate monitoring of organ system functions is desirable.

Usage in Newborns and Infants

This product contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants.

The potential for the toxic effect in the pediatric population from chemicals that may leach from the single dose premixed IV preparation in plastic has not been evaluated.

Geriatric Use

Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. However, other reported clinical experience indicates that antibiotic-associated colitis and diarrhea (due to *Clostridium difficile*) seen in association with most antibiotics occur more frequently in the elderly (>60 years) and may be more severe. These patients should be carefully monitored for the development of diarrhea.

Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration.

ADVERSE REACTIONS

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

Gastrointestinal: Antibiotic-associated colitis (see **WARNINGS**), pseudomembranous colitis, abdominal pain, nausea, and vomiting. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see **WARNINGS**). An unpleasant or metallic taste occasionally has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all 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, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions.

Skin and Mucous Membranes: Pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported (see *Hypersensitivity 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.

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

Musculoskeletal: Rare instances of polyarthritis have

Cardiovascular: Rare instances of cardiopulmonary
been reported following too rapid intravenous admini
ADMINISTRATION section.)

OVERDOSAGE

Significant mortality was observed in mice at an int
and in rats at an oral or subcutaneous dose of appr
mice, convulsions and depression were observed.

Hemodialysis and peritoneal dialysis are not effec
from the serum.

ANIMAL TOXICOLOGY

One year oral toxicity studies in Spartan Sprague-Da
dose levels up to 300 mg/kg/day (approximately 1.1 ar
ommended adult human dose based on mg/m^2, res
damycin to be well tolerated. No appreciable differenc
been observed between groups of animals treated with
control groups. Rats receiving clindamycin hydrochlorid
imately 2.1 times the highest recommended adult huma
6 months tolerated the drug well; however, dogs dosed
7.2 times the highest recommended adult human dos
would not eat, and lost weight.

DOSAGE AND ADMINISTRATION

If diarrhea occurs during therapy, this antibiotic s
WARNING box).

Adults: Parenteral (IM or IV Administration): Seriou
gram-positive cocci and the more susceptible anaerob
Bacteroides fragilis, *Peptococcus* species and *Clos*
Clostridium perfringens):

600-1200 mg/day in 2, 3 or 4 equal doses.

More severe infections, particularly those due to prov
fragilis, *Peptococcus* species, or *Clostridium* spec
perfringens:

1200-2700 mg/day in 2, 3 or 4 equal doses.

For more serious infections, these doses may have to
ening situations due to either aerobes or anaerobes the
Doses of as much as 4800 mg daily have been given
Dilution and Infusion Rates section below.

Single intramuscular injections of greater than 600 mg

Alternatively, drug may be administered in the form
the first dose followed by continuous IV infusion as follo

To maintain serum clindamycin levels	Rapid infusion rate
Above 4 mcg/mL	10 mg/min for 30 min
Above 5 mcg/mL	15 mg/min for 30 min
Above 6 mcg/mL	20 mg/min for 30 min

Neonates (less than 1 month):

15 to 20 mg/kg/day in 3 to 4 equal doses. The lowe
for small prematures.

Pediatric patients 1 month of age to 16 years: Paren
tion: 20 to 40 mg/kg/day in 3 or 4 equal doses. The high
more severe infections. As an alternative to dosing on a
may be dosed on the basis of square meters body surfa
ous infections and 450 mg/m^2/day for more severe infect

Parenteral therapy may be changed to oral CLEOC
Granules (clindamycin palmitate hydrochloride) or CLE
damycin hydrochloride) when the condition warrants a
physician.

In cases of β-hemolytic streptococcal infections, trea
for at least 10 days.

**Dilution and Infusion Rates: Clindamycin phosphate
IV administration. The concentration of clindamycin
should not exceed 18 mg per mL. Infusion rates shou
minute.** The usual infusion dilutions and rates are as foll

Dose	Diluent
300 mg	50 mL
600 mg	50 mL
900 mg	50-100 mL
1200 mg	100 mL

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clindamycin phosphate injection in 5% dextro**

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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.

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** section.)

OVERDOSAGE

Significant mortality was observed in mice at an intravenous dose of 855 mg/kg and in rats at an oral or subcutaneous dose of approximately 2618 mg/kg. In the mice, convulsions and depression were observed.

Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

ANIMAL TOXICOLOGY

One year oral toxicity studies in Spartan Sprague-Dawley rats and beagle dogs at dose levels up to 300 mg/kg/day (approximately 1.1 and 3.6 times the highest recommended adult human dose based on mg/m^2, respectively) have shown clindamycin to be well tolerated. No appreciable difference in pathological findings has been observed between groups of animals treated with clindamycin and comparable control groups. Rats receiving clindamycin hydrochloride at 600 mg/kg/day (approximately 2.1 times the highest recommended adult human dose based on mg/m^2) for 6 months tolerated the drug well; however, dogs dosed at this level (approximately 7.2 times the highest recommended adult human dose based on mg/m^2) vomited, would not eat, and lost weight.

DOSAGE AND ADMINISTRATION

If diarrhea occurs during therapy, this antibiotic should be discontinued (see **WARNING** box).

Adults: Parenteral (IM or IV Administration): Serious infections due to aerobic gram-positive cocci and the more susceptible anaerobes (NOT generally including *Bacteroides fragilis*, *Peptococcus* species and *Clostridium* species other than *Clostridium perfringens*):

600-1200 mg/day in 2, 3 or 4 equal doses.

More severe infections, particularly those due to proven or suspected *Bacteroides fragilis*, *Peptococcus* species, or *Clostridium* species other than *Clostridium perfringens*:

1200-2700 mg/day in 2, 3 or 4 equal doses.

For more serious infections, these doses may have to be increased. In life-threatening situations due to either aerobes or anaerobes these doses may be increased. Doses of as much as 4800 mg daily have been given intravenously to adults. See **Dilution and Infusion Rates** section below.

Single intramuscular injections of greater than 600 mg are not recommended.

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

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

Neonates (less than 1 month):

15 to 20 mg/kg/day in 3 to 4 equal doses. The lower dosage may be adequate for small prematures.

Pediatric patients 1 month of age to 16 years: Parenteral (IM or IV) administration: 20 to 40 mg/kg/day in 3 or 4 equal doses. The higher doses would be used for more severe infections. 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.

Parenteral therapy may be changed to oral CLEOCIN PEDIATRIC® Flavored Granules (clindamycin palmitate hydrochloride) or CLEOCIN HCl® Capsules (clindamycin hydrochloride) when the condition warrants and at the discretion of the physician.

In cases of β-hemolytic streptococcal infections, treatment should be continued for at least 10 days.

Dilution and Infusion Rates: Clindamycin phosphate must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL. Infusion rates should not exceed 30 mg per minute. The usual infusion dilutions and rates are as follows:

Dose	Diluent	Time
300 mg	50 mL	10 min
600 mg	50 mL	20 min
900 mg	50-100 mL	30 min
1200 mg	100 mL	40 min

Cleocin Phosphate

brand of clindamycin phosphate injection, USP and clindamycin phosphate injection in 5% dextrose

Administration of more than 1200 mg in a single 1-hour infusion

Parenteral drug products should be inspected visually for c discoloration prior to administration, whenever solution and co

Dilution and Compatibility: Physical and biological compatibi for 24 hours at room temperature have demonstrated no inact bility with the use of CLEOCIN PHOSPHATE Sterile Solution phate) in IV solutions containing sodium chloride, glucose, c and solutions containing vitamin B complex in concentration cally. No incompatibility has been demonstrated with the an kanamycin, gentamicin, penicillin or carbenicillin.

The following drugs are physically incompatible with clin ampicillin sodium, phenytoin sodium, barbiturates, aminoph conate, and magnesium sulfate.

The compatibility and duration of stability of drug admixtures on concentration and other conditions. For current information ities of clindamycin phosphate under specific conditions, please and Drug Information Unit, Pharmacia & Upjohn Company.

Physico-Chemical Stability of diluted solutions of CLEOCIN

Room temperature: 6, 9 and 12 mg/mL (equivalent to c dextrose injection 5%, sodium chloride injection 0.9%, or Lacta in glass bottles or minibags, demonstrated physical and che least 16 days at 25° C. Also, 18 mg/mL (equivalent to clindamyc injection 5%, in minibags, demonstrated physical and chemica 16 days at 25° C.

Refrigeration: 6, 9 and 12 mg/mL (equivalent to clindamyc injection 5%, sodium chloride injection 0.9%, or Lactated Ringe bottles or minibags, demonstrated physical and chemical stat days at 4° C.

IMPORTANT: This chemical stability information in no way in be acceptable practice to use this product well after the prepara fessional practice suggests that compounded admixtures should soon after preparation as is feasible.

Frozen: 6, 9 and 12 mg/mL (equivalent to clindamycin base 5%, sodium chloride injection 0.9%, or Lactated Ringers In demonstrated physical and chemical stability for at least eight w

Frozen solutions should be thawed at room temperature and r

DIRECTIONS FOR DISPENSING

Pharmacy Bulk Package — Not for Direct Infus

The Pharmacy Bulk Package is for use in a Pharmacy Adm under a laminar flow hood. Entry into the vial should be made w sterile transfer set or other small diameter sterile dispensing d dispensed in aliquots using aseptic technique. Multiple entries syringe are not recommended. AFTER ENTRY USE ENTIRE C PROMPTLY. ANY UNUSED PORTION MUST BE DISCARDED AFTER INITIAL ENTRY.

DIRECTIONS FOR USE

CLEOCIN PHOSPHATE IV Solution in Galaxy Plastic Contai

Premixed CLEOCIN PHOSPHATE IV Solution is for intravei using sterile equipment. Check for minute leaks prior to use firmly. If leaks are found, discard solution as sterility may be im supplementary medication. Parenteral drug products should be for particulate matter and discoloration prior to administration and container permit. Do not use unless solution is clear and se

Caution: Do not use plastic containers in series connection result in air embolism due to residual air being drawn from the before administration of the fluid from the secondary container is

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accomp

Preparation of CLEOCIN PHOSPHATE in ADD-Vantage Sys

Only. CLEOCIN PHOSPHATE 600 mg and 900 mg may be recon 100 mL, respectively, of Dextrose Injection 5% or Sodium Chlori the ADD-diluent container. Refer to separate instructions for ADD

HOW SUPPLIED

Each mL of CLEOCIN PHOSPHATE Sterile Solution contains phate equivalent to 150 mg clindamycin; 0.5 mg disodium edeta alcohol added as preservative. When necessary, pH is adju hydroxide and/or hydrochloric acid. CLEOCIN PHOSPHATE following packages:

25-2 mL vials	N
25-4 mL vials	N
25-6 mL vials	N
1-60 mL Pharmacy Bulk Package	N

leocin Phosphate

nd of clindamycin phosphate injection, USP and
ndamycin phosphate injection in 5% dextrose

Administration of more than 1200 mg in a single 1-hour infusion is not recommended.

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

Dilution and Compatibility: Physical and biological compatibility studies monitored for 24 hours at room temperature have demonstrated no inactivation or incompatibility with the use of CLEOCIN PHOSPHATE Sterile Solution (clindamycin phosphate) in IV solutions containing sodium chloride, glucose, calcium or potassium, and solutions containing vitamin B complex in concentrations usually used clinically. No incompatibility has been demonstrated with the antibiotics cephalothin, kanamycin, gentamicin, penicillin or carbenicillin.

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

The compatibility and duration of stability of drug admixtures will vary depending on concentration and other conditions. For current information regarding compatibilities of clindamycin phosphate under specific conditions, please contact the Medical and Drug Information Unit, Pharmacia & Upjohn Company.

Physico-Chemical Stability of diluted solutions of CLEOCIN PHOSPHATE

Room temperature: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or Lactated Ringers Injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 16 days at 25° C. Also, 18 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, in minibags, demonstrated physical and chemical stability for at least 16 days at 25° C.

Refrigeration: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or Lactated Ringers Injection in glass bottles or minibags, demonstrated physical and chemical stability for at least 32 days at 4° C.

IMPORTANT: This chemical stability information in no way indicates that it would be acceptable practice to use this product well after the preparation time. Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Frozen: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in dextrose injection 5%, sodium chloride injection 0.9%, or Lactated Ringers Injection in minibags ·nstrated physical and chemical stability for at least eight weeks at -10° C.
en solutions should be thawed at room temperature and not refrozen.

.CTIONS FOR DISPENSING

Pharmacy Bulk Package — Not for Direct Infusion

The Pharmacy Bulk Package is for use in a Pharmacy Admixture Service only under a laminar flow hood. Entry into the vial should be made with a small diameter sterile transfer set or other small diameter sterile dispensing device, and contents dispensed in aliquots using aseptic technique. Multiple entries with a needle and syringe are not recommended. AFTER ENTRY USE ENTIRE CONTENTS OF VIAL PROMPTLY. ANY UNUSED PORTION MUST BE DISCARDED WITHIN 24 HOURS AFTER INITIAL ENTRY.

DIRECTIONS FOR USE

CLEOCIN PHOSPHATE IV Solution in Galaxy Plastic Container

Premixed CLEOCIN PHOSPHATE IV Solution is for intravenous administration using sterile equipment. Check for minute leaks prior to use by squeezing bag firmly. If leaks are found, discard solution as sterility may be impaired. Do not add supplementary medication. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use unless solution is clear and seal is intact.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Preparation of CLEOCIN PHOSPHATE in ADD-Vantage System—For IV Use Only. CLEOCIN PHOSPHATE 600 mg and 900 mg may be reconstituted in 50 mL or 100 mL, respectively, of Dextrose Injection 5% or Sodium Chloride Injection 0.9% in the ADD-diluent container. Refer to separate instructions for ADD-Vantage‡ System.

HOW SUPPLIED

Each mL of CLEOCIN PHOSPHATE Sterile Solution contains clindamycin phosphate equivalent to 150 mg clindamycin; 0.5 mg disodium edetate; 9.45 mg benzyl alcohol added as preservative. When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid. CLEOCIN PHOSPHATE is available in the following packages:

25-2 mL vials	NDC 0009-0870-21
25-4 mL vials	NDC 0009-0775-26
25-6 mL vials	NDC 0009-0902-11
1-60 mL Pharmacy Bulk Package	NDC 0009-0728-05

Cleocin Phosphate

brand of clindamycin phosphate injection, USP and
clindamycin phosphate injection in 5% dextrose

CLEOCIN PHOSPHATE is supplied in ADD-Vantage vials as follows:

NDC	Vial Size	Total Clindamycin Phosphate/vial	Amount of Diluent
0009-3124-01	4 mL	600 mg	50 mL
0009-3447-01	6 mL	900 mg	100 mL

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

(continued below)

CLEOCIN PHOSPHATE IV Solution in Galaxy plastic containers is a sterile solution of clindamycin phosphate with 5% dextrose. The single dose Galaxy plastic containers are available as follows:

24-300 mg/50 mL containers	NDC 0009-3381-01
24-600 mg/50 mL containers	NDC 0009-3375-01
24-900 mg/50 mL containers	NDC 0009-3382-01

Exposure of pharmaceutical products to heat should be minimized. It is recommended that Galaxy plastic containers be stored at room temperature (25° C). Avoid temperatures above 30° C.

Caution: Federal law prohibits dispensing without prescription.

Pharmacia & Upjohn Company • Kalamazoo, MI 49001, USA

Revised December 1997 810 020 033
691273

REFERENCES

1. Smith RB, Phillips JP: Evaluation of CLEOCIN HCl and CLEOCIN Phosphate in an Aged Population. Upjohn TR 8147-82-9122-021, December 1982.
2. Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic susceptibility testing by a standardized single disk method. *Am. J. Clin. Path.*, 45:493-496, 1966. Standardized Disk Susceptibility Test, *Federal Register*, 37:20527-29, 1972.
3. 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.

‡ ADD-Vantage is a registered trademark of Abbott Laboratories.

CLEOCIN PHOSPHATE IV Solution in the Galaxy plastic containers is manufactured for Pharmacia & Upjohn Company by Baxter Healthcare Corporation, Deerfield, IL 60015.

Galaxy® is a registered trademark of Baxter International, Inc.

NDC 0074-9621-13

mL 12 Single-dose containers

lindamycin
ıjection
5% Dextrose

300 mg*/50 mL

r I.V. Use

*Each 50 mL contains: clindamycin phosphate equivalent to 300 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide or hydrochloric acid for pH adjustment.
Usual dosage: See insert. Sterile, nonpyrogenic. Do not add supplementary medication.
Check for minute leaks and solution clarity. Must not be used in series connections.
Recommended storage: Room temperature (25°C). Avoid temperatures above 30°C.
See package insert for complete product information. Protect from freezing.

℞ only

(01) 1 030074 962113 7

08-9306-2/R1-4/00
Printed in USA
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

50 mL 12 Single-dose containers

Clindamycin Injection
in 5% Dextrose

300 mg*/50 mL

For I.V. Use

NDC 0074-9621-13

NDC 0074-9621-13

50 mL 12 Single-dose containers

Clindamycin Injection
in 5% Dextrose

300 mg*/50 mL

For I.V. Use

APPROVED
JUN 29 2000

50 mL 12 Single-dose containers

Clindamycin Injection
in 5% Dextrose

300 mg*/50 mL

For I.V. Use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

NDC 0074-9621-13

NDC 0074-9621-13

50 mL 12 Single-dose containers

Clindamycin Injection
in 5% Dextrose

300 mg*/50 mL

For I.V. Use

*Each 50 mL contains: clind
dextrose hydrous, USP with
or hydrochloric acid for pH
Usual dosage: See insert. S
Check for minute leaks and
Recommended storage: Ro
See package insert for con

℞ only

ABBOTT LABORATORIES, NORTH

50 mL 12 Single-dose containers

NDC 0074-9622-13

Clindamycin Injection in 5% Dextrose

600 mg*/50 mL

For I.V. Use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

50 mL 12 Single-dose containers

Clindamycin Injection in 5% Dextrose

600 mg*/50 mL

For I.V. Use

NDC 0074-9622-13

*Each 50 mL contains: clindamycin phosphate equivalent to 600 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide or hydrochloric acid for pH adjustment.

Usual dosage: See insert. Sterile, nonpyrogenic. Do not add supplementary medication.

Check for minute leaks and solution clarity. Must not be used in series connections.

Recommended storage: Room temperature (25°C). Avoid temperatures above 30°C.

See package insert for complete product information. Protect from freezing.

℞ only

(01) 1 030074 962213 4

08-9309-2/R1-4/00

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Printed in USA

NDC 0074-9622-13

12 Single-dose containers

ndamycin
ection
% Dextrose

00 mg*/50 mL

I.V. Use

NDC 0074-9622-13

50 mL 12 Single-dose containers

Clindamycin Injection

JUN 29 2007

APPROVED

in 5% Dextrose

600 mg*/50 mL

For I.V. Use

lindamycin phosphate equivalent to 600 mg clindamycin and 2.5 g
vith 2 mg edetate disodium, USP added. May contain sodium hydroxide
pH adjustment.
t. Sterile, nonpyrogenic. Do not add supplementary medication.
and solution clarity. Must not be used in series connections.
Room temperature (25°C). Avoid temperatures above 30°C.
complete product information. Protect from freezing.

(01) 1 030074 962213 4

08-9309-2/R1-4/00

Printed in USA

IRTH CHICAGO, IL 60064, USA

50 mL 12 Single-dose containers

Clindamycin Injection

in 5% Dextrose

600 mg*/50 mL

For I.V. Use

NDC 0074-9623-13

50 mL 12 Single-dose containers

Clindamycin Injection
in 5% Dextrose

[redacted]

For I.V. Use

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

50 mL 12 Single-dose containers

NDC 0074-9623-13

Clindamycin Injection in 5% Dextrose

[redacted]

For I.V. Use

NDC 0074-9623-13

2 Single-dose containers

damycin ction Dextrose

[redacted]

Use

*Each 50 mL contains: clindamycin phosphate equivalent to 900 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide or hydrochloric acid for pH adjustment.

Usual dosage: See insert. Sterile, nonpyrogenic. Do not add supplementary medication.

Check for minute leaks and solution clarity. Must not be used in series connections.

Recommended storage: Room temperature (25°C). Avoid temperatures above 30°C.

See package insert for complete product information. Protect from freezing.

℞ only

(01) 1 030074 962313 1

08-9311-2/R1-4/00

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Printed in USA

NDC 0074-9623-13

50 mL 12 Single-dose containers

Clindamycin Injection

in 5% Dextrose

JUN 29 2001

[redacted]

For I.V. Use

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50 mL 12 Single-dose containers

Clindamycin Inject

in 5% Dextrose

[redacted]

For I.V. Use

osphate equivalent to 900 mg clindamycin and 2.5 g
ate disodium, USP added. May contain sodium hydroxide
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yrogenic. Do not add supplementary medication.
arity. Must not be used in series connections.
ature (25°C). Avoid temperatures above 30°C.
uct information. Protect from freezing.

(01) 1 030074 962313 1

08-9311-2/R1-4/00

Printed in USA

60064, USA

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ɔin Injection

ɒse

[redacted]

0, IL 60064, USA

NDC 0074-9623-13

NDC 0074-9623-13

50 mL 12 Single-dose containers

Clindamycin Injection

in 5% Dextrose

[redacted]

For I.V. Use

Front

50 mL Single-dose container NDC 0074-9623-13

Clindamycin Injection

in 5% Dextrose

[redacted]

*Each 50 mL contains: clindamycin phosphate equivalent to 900 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide or hydrochloric acid for pH adjustment.

For I.V. use only.

Usual dosage: See insert. Sterile, nonpyrogenic. Do not add supplementary medication. Check for minute leaks and solution clarity. Must not be used in series connections.

Recommended storage: Room temperature (25°C). Avoid temperatures above 30°C. Protect from freezing.

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7 OTHER

LATEX

50-3983-2/R1-4/00 Printed in USA

Abbott Laboratories, North Chicago, IL 60064, USA

Back

Clindamycin Injection

in 5% Dextrose

[redacted]

(01) 0 30074 962313 4

Front

50 mL Single-dose container NDC 0074-9622-13

Clindamycin Injection in 5% Dextrose

JUN 29 2001 APPROVED

600 mg*/50 mL

*Each 50 mL contains: clindamycin phosphate equivalent to 600 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide or hydrochloric acid for pH adjustment.

For I.V. use only.

Usual dosage: See insert. Sterile, nonpyrogenic. Do not add supplementary medication. Check for minute leaks and solution clarity. Must not be used in series connections.

Recommended storage: Room temperature (25°C). Avoid temperatures above 30°C. Protect from freezing.

℞ only

7 OTHER

LATEX

50-3981-2/R1-4/00 Printed in USA

Abbott Laboratories, North Chicago, IL 60064, USA

Back

Clindamycin Injection in 5% Dextrose

JUN 29 2001 APPROVED

600 mg*/50 mL

(01) 0 30074 962213 7

Front

50 mL Single-dose container NDC 0074-9622-13

Clindamycin Injection
in 5% Dextrose

JUN 29 2001 APPROVED

600 mg*/50 mL

*Each 50 mL contains: clindamycin phosphate equivalent to 600 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide or hydrochloric acid for pH adjustment.

For I.V. use only.

Usual dosage: See insert. Sterile, nonpyrogenic. Do not add supplementary medication. Check for minute leaks and solution clarity. Must not be used in series connections.

Recommended storage: Room temperature (25°C). Avoid temperatures above 30°C. Protect from freezing.

℞ only

7 OTHER

DEHP

50-3981-2/R1-4/00 Printed in USA

Abbott Laboratories, North Chicago, IL 60064, USA

Back

Clindamycin Injection APPROVED

in 5% Dextrose

JUN 29 2001

600 mg*/50 mL

(01) 0 30074 962213 7

Front

50 mL Single-dose container NDC 0074-9621-13

Clindamycin Injection

in 5% Dextrose

JUN 29 2001 APPROVED

300 mg*/50 mL

*Each 50 mL contains: clindamycin phosphate equivalent to 300 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide or hydrochloric acid for pH adjustment.

For I.V. use only.

Usual dosage: See insert. Sterile, nonpyrogenic. Do not add supplementary medication. Check for minute leaks and solution clarity. Must not be used in series connections.

Recommended storage: Room temperature (25°C). Avoid temperatures above 30°C. Protect from freezing.

℞ only

7 OTHER

LATEX

50-3982-2/R1-4/00 Printed in USA

Abbott Laboratories, North Chicago, IL 60064, USA

Back

Clindamycin Injection APPROVED

in 5% Dextrose

300 mg*/50 mL

(01) 0 030074 962113 0

65-027
AP 6/25/01

Clindamycin Injection in 5% Dextrose

For Intravenous Use Only

WARNING

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

Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS AND USAGE section. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.

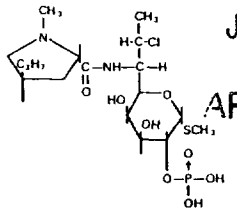
DESCRIPTION

Clindamycin Injection in 5% Dextrose contains clindamycin phosphate, a water soluble ester of clindamycin and phosphoric acid. Each 50 mL contains: clindamycin phosphate equivalent to 300 mg, 600 mg, or 900 mg clindamycin and 2.5 g dextrose hydrous, USP with 2 mg edetate disodium, USP added. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH is 5.8 range 5.5 to 7.0. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7 (R)-hydroxyl group of the parent compound lincomycin. Clindamycin Injection in 5% Dextrose is for intravenous use only.

The chemical name of clindamycin phosphate is 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), (2*S*-*trans*)-.

The molecular formula is $C_{18}H_{34}ClN_2O_8PS$ and the molecular weight is 504.97.

The structural formula is represented below:



The plastic container is fabricated from a specially designed form fill seal multilayer plastic. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period. The suitability or the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Biologically inactive clindamycin phosphate is rapidly converted 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 elimination half-life is 6 minutes; however, the serum elimination half-life of active clindamycin is about 3 hours in adults and 2½ hours in pediatric patients.

After intramuscular injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in pediatric patients. Serum level curves may be constructed from IV peak serum levels as given in Table 1 by application of elimination half-lives listed above.

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 to 12 hours in adults and every 6 to 8 hours in pediatric patients, or by continuous intravenous infusion. An equilibrium state is reached by the third dose.

The elimination half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Dosage schedules need not be modified in the presence of mild or moderate renal or hepatic disease.

No significant levels of clindamycin are attained in the cerebrospinal fluid even in the presence of inflamed meninges.

Pharmacokinetic studies in elderly volunteers (61 to 79 years) and younger adults (18 to 39 years) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentration-time curve) after IV administration of clindamycin phosphate. After oral administration of clindamycin hydrochloride, elimination half-life is increased to approximately 4 hours (range 3.4 to 5.1 h) in the elderly compared to 3.2 hours (range 2.1 to 4.2 h) in younger adults. The extent of absorption, however, is not different between the age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function[1].

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

Table 1
Average Peak and Trough Serum Concentrations of Active Clindamycin After Dosing with Clindamycin Phosphate

Dosage Regimen	Peak mcg/mL	Trough mcg/mL
Healthy Adult Males (Post equilibrium)		
600 mg IV in 30 min q6h	10.9	2.0
600 mg IV in 30 min q8h	10.8	1.1
900 mg IV in 30 min q8h	14.1	1.7
600 mg IM q12*	9	
Children (first dose)*		
5-7 mg/kg IV in 1 hour	10	
5-7 mg/kg IM	8	
3-5 mg/kg IM	4	

*Data in this group from patients being treated for infection.

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 (penicillinase and non-penicillinase producing strains).
Staphylococcus epidermidis 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 anaerobes to clindamycin. Most *Clostridium perfringens* are susceptible, but other species, e.g., *Clostridium sporogenes* and *Clostridium tertium* are frequently resistant to clindamycin. Susceptibility testing should be done.

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

***In Vitro* Susceptibility Testing:**

Disk diffusion technique-Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure[2] has been recommended for use with disks to test susceptibility to clindamycin.

Reports from a laboratory using the standardized single-disk susceptibility test[1] with a 2 mcg clindamycin disk should be interpreted according to the following criteria:

Susceptible organisms produce zones of 17 mm or greater, indicating that the tested organism is likely to respond to therapy.

Organisms of intermediate susceptibility produce zones of 15 – 16 mm, indicating that the tested organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Standardized procedures require the use of control organisms. The 2 mcg clindamycin disk should give a zone diameter between 24 and 30 mm for *S. aureus* ATCC 25923.

Dilution techniques — A bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) for clindamycin is not more than 1.6 mcg/mL. Organisms are considered moderately susceptible if the MIC is greater than 1.6 mcg/mL and less than or equal to 4.8 mcg/mL. Organisms are considered resistant if the MIC is greater than 4.8 mcg per mL.

The range of MICs for the control strains are as follows:

S. aureus ATCC 29213, 0.06 to 0.25 mcg/mL.

E. faecalis ATCC 29212, 4.0 to 16 mcg/mL.

For anaerobic bacteria the minimum inhibitory concentration (MIC) of clindamycin can be determined by agar dilution and broth dilution (including microdilution) techniques.[3] If MICs are not determined routinely, the disk broth method is recommended for routine use. THE KIRBY-BAUER DISK DIFFUSION METHOD AND ITS INTERPRETIVE STANDARDS ARE NOT RECOMMENDED FOR ANAEROBES.

INDICATIONS AND USAGE

Clindamycin Injection is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin Injection is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of antibiotic-associated pseudomembranous colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less toxic alternatives (e.g., erythromycin).

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

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

Clindamycin Injection is indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower respiratory tract infections including pneumonia, empyema, and lung abscess caused by anaerobes, *Streptococcus pneumoniae,* other streptococci (except *E. 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 infection 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.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

WARNINGS

See WARNING box.

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

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

Usage in Meningitis — Since clindamycin does not diffuse

adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General

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.

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

Clindamycin Injection should be prescribed with caution in atopic individuals.

Certain infections may require incision and drainage or other indicated surgical procedures in addition to antibiotic therapy.

The use of Clindamycin Injection may result in overgrowth of nonsusceptible organisms — particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin Injection should not be injected intravenously undiluted as a bolus, but should be infused over at least 10 – 60 minutes as directed in the **DOSAGE AND ADMINISTRATION** section.

Clindamycin dosage modification may not be necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of clindamycin half-life has been found. However, it was postulated from studies that when given every eight hours, accumulation should rarely occur. Therefore, dosage modification in patients with liver disease may not be necessary. However, periodic liver enzyme determinations should be made when treating patients with severe liver disease.

Laboratory Tests

During prolonged therapy periodic liver and kidney function tests and blood counts should be performed.

Drug Interactions

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.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (2.1 and 1.1 times the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (0.9 and 0.5 times the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if it is clearly needed.

Nursing Mothers

Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for adverse reactions due to clindamycin in neonates (see Pediatric Use), the decision to discontinue the drug should be made, taking into account the importance of the drug to the mother.

Pediatric Use

When Clindamycin Injection is administered to the pediatric population (birth to 16 years) appropriate monitoring of organ system functions is desirable.

Usage in Newborns and Infants

The potential for the toxic effect in pediatric patients from chemicals that may leach from the single dose premixed IV preparation in plastic has not been evaluated.

Geriatric Use

Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. However, other reported clinical experience indicates that antibiotic-associated colitis and diarrhea (due to *Clostridium difficile*) seen in association with most antibiotics occur more frequently in the elderly (>60 years) and may be more severe. These patients should be carefully monitored for the development of diarrhea.

Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration.

ADVERSE REACTIONS

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

Gastrointestinal: Antibiotic-associated colitis (see WARNINGS), pseudomembranous colitis, abdominal pain, nausea and vomiting. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see WARNINGS). An unpleasant or metallic taste occasionally has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reactions: Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all 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, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions.

Skin and Mucous Membranes: Pruritus, vaginitis, and rare instances of exfoliative dermatitis have been reported. (See *Hypersensitivity 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.

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.

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 section).

OVERDOSAGE

Significant mortality was observed in mice at an intravenous dose of 855 mg/kg and in rats at an oral or subcutaneous dose of approximately 2618 mg/kg. In the mice, convulsions and depression were observed.

Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

DOSAGE AND ADMINISTRATION

Dosing references to the intramuscular route of administration are for informational purposes only.

If diarrhea occurs during therapy, this antibiotic should be discontinued. (See WARNING box.)

Adults: Parenteral (IM or IV Administration): Serious infections due to aerobic gram-positive cocci and the more susceptible anaerobes (NOT generally including *Bacteroides fragilis, Peptococcus* species and *Clostridium* species other than *Clostridium perfringens*):

600 – 1200 mg/day in 2, 3 or 4 equal doses.

More severe infections, particularly those due to proven or suspected *Bacteroides fragilis, Peptococcus* species, or *Clostridium* species other than *Clostridium perfringens*:

1200 – 2700 mg/day in 2, 3 or 4 equal doses.

For more serious infections, these doses may have to be increased. In life-threatening situations due to either aerobes or anaerobes, these doses may be increased. Doses of as much as 4800 mg daily have been given intravenously to adults. See **Infusion Rates** section below.

Single intramuscular injections of greater than 600 mg are not recommended.

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

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

Neonates (less than 1 month): 15 to 20 mg/kg/day in 3 to 4 equal doses. The lower dosage may be adequate for small prematures.

Pediatric patients (1 month of age to 16 years): Parenteral (IM or IV) administration: 20 to 40 mg/kg/day in 3 or 4 equal doses. The higher doses would be used for more severe infections. 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.

Parenteral therapy may be changed to oral clindamycin palmitate hydrochloride or clindamycin hydrochloride capsules when the condition warrants and at the discretion of the physician.

In cases of ß-hemolytic streptococcal infections, treatment should be continued for at least 10 days.

Infusion Rates: Infusion rates should not exceed 30 mg per minute. The usual infusion rates are as follows:

Dose	Time
300 mg	10 min
600 mg	20 min
900 mg	30 min

Administration of more than 1200 mg in a single 1-hour infusion is not recommended.

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

No incompatibility has been demonstrated with the antibiotics cephalothin, kanamycin, gentamicin, penicillin or carbenicillin.

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

Directions For Use

Clindamycin Injection in 5% Dextrose in form fill seal plastic container is for intravenous administration using sterile equipment. Check for minute leaks prior to use by squeezing bag firmly. If leaks are found, discard solution as sterility may be impaired. Do not add supplementary medication. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use unless solution is clear and seal is intact.

Caution: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions of accompanying set.

HOW SUPPLIED

Clindamycin Injection in 5% Dextrose is supplied in single-dose form fill seal plastic flexible containers as follows:

List	Quantity per carton	Concentration equivalent to Clindamycin
9621	12 – 50 mL	300 mg/50 mL
9622	12 – 50 mL	600 mg/50 mL
9623	12 – 50 mL	900 mg/50 mL

Exposure of pharmaceutical products to heat should be minimized. It is recommended that plastic containers be stored at room temperature (25°C). Avoid temperatures above 30°C.

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