Cleocin HCl®

clindamycin hydrochloride
capsules, USP

PHARMACIA

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

Cleocin HCl
clindamycin
hydrochloride
capsules, USP

0810570928

Cleocin HCl
clindamycin
hydrochloride
capsules, USP

0810570928

Cleocin HCl

**brand of clindamycin
hydrochloride capsules, USP**

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.

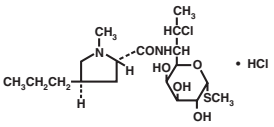
DESCRIPTION

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

CLEOCIN HCl Capsules contain clindamycin hydrochloride equivalent to 75 mg, 150 mg or 300 mg of clindamycin.

Inactive ingredients: **75 mg**—corn starch, FD&C blue no. 1, FD&C yellow no. 5, gelatin, lactose, magnesium stearate and talc; **150 mg**—corn starch, FD&C blue no. 1, FD&C yellow no. 5, gelatin, lactose, magnesium stearate, talc and titanium dioxide; **300 mg**—corn starch, FD&C blue no. 1, gelatin, lactose, magnesium stearate, talc and titanium dioxide.

The structural formula is represented below:



The chemical name for clindamycin hydrochloride is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside monohydrochloride.

CLINICAL PHARMACOLOGY

Human Pharmacology: Serum level studies with a 150 mg oral dose of clindamycin hydrochloride in 24 normal adult volunteers showed that clindamycin was rapidly absorbed after oral administration. An average peak serum level of 2.50 mcg/mL was reached in 45 minutes; serum levels averaged 1.51 mcg/mL at 3 hours and 0.70 mcg/mL at 6 hours. Absorption of an oral dose is virtually complete (90%), and the concomitant administration of food does not appreciably modify the serum concentrations; serum levels have been uniform and predictable from person to person and dose to dose. Serum level studies following multiple doses of CLEOCIN HCl for up to 14 days show no evidence of accumulation or altered metabolism of drug.

Serum half-life of clindamycin is increased slightly in patients with markedly reduced renal function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

Concentrations of clindamycin in the serum increased linearly with increased dose. Serum levels exceed the MIC (minimum inhibitory concentration) for most indicated organisms for at least six hours following administration of the usually recommended doses. Clindamycin is widely distributed in body fluids and tissues (including bones). The average biological half-life is 2.4 hours. Approximately 10% of the bioactivity is excreted in the urine and 3.6% in the feces; the remainder is excreted as bioinactive metabolites.

Doses of up to 2 grams of clindamycin per day for 14 days have been well tolerated by healthy volunteers, except that the incidence of gastrointestinal side effects is greater with the higher doses.

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.

Microbiology: Clindamycin inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It has activity against Gram-positive aerobes and anaerobes as well as the Gram-negative anaerobes. Clindamycin is bacteriostatic. Cross-resistance between clindamycin and lincomycin is complete. Antagonism *in vitro* has been demonstrated between clindamycin and erythromycin.

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

Gram-positive aerobes
Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Anaerobes
Prevotella melaninogenica
Fusobacterium necrophorum
Fusobacterium nucleatum
Peptostreptococcus anaerobius
Clostridium perfringens

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for clindamycin. However, the safety and effectiveness of clindamycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive aerobes
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus oralis
Streptococcus mitis

Anaerobes
Prevotella intermedia
Prevotella bivia
Propionibacterium acnes
Micromonas ("Peptostreptococcus") micros
Finegoldia ("Peptostreptococcus") magna
Actinomyces israelii
Clostridium clostridioforme
Eubacterium lentum

SUSCEPTIBILITY TESTING METHODS:

NOTE: Susceptibility testing by dilution methods requires the use of clindamycin susceptibility powder.

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth and agar)[1,2,3] or equivalent with standardized inoculum concentrations and standardized concentrations of clindamycin powder.The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques: Quantitative methods that require the measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 2 mcg of clindamycin to test the susceptibility of microorganisms to clindamycin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility Interpretive Criteria for Clindamycin

Pathogen	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in mcg/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Staphylococcus spp.	≤0.5	1-2	≥4	≥21	15-20	≤14
Streptococcus pneumoniae and other *Streptococcus* spp.	≤0.25[a]	0.5	≥1	≥19[b]	16-18	≤15
Anaerobic Bacteria[c]	≤2	4	≥8	NA	NA	NA

[a] These interpretive standards for *S. pneumoniae* and other *Streptococcus* spp. are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

[b] These zone diameter interpretive standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20 to 24 hours.

[c] These interpretive criteria are for all anaerobic bacterial pathogens; no organism specific interpretive criteria are available. NA=not applicable

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard clindamycin powder should provide the following range of values noted in Table 2. **NOTE:** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table 2. Acceptable Quality Control Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in mcg/mL)	Disk Diffusion (Zone Diameters in mm)
When Testing Aerobic Pathogens		
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619[d]	0.03–0.12[e]	19–25[f]

(continued)

Pfizer

Composition Unit 2566

Black

COMPOSITION ORDER #	PRODUCT		COPY CODE #
22685	CLEOCIN HCL		810 570 928
CCS #	NDC #	EDP #	ITEM
0225-01	0009-0225-01	692851	Insert
BOTTLE #	SIZE	FOLDED SIZE	DRAWING #
	10 x 10"	2.5 x 1"	PD2364
ADDITIONAL INFORMATION		DATE	TYPESET BY
spine 4" from bottom		12/09/03	KL/DHUFF

Cleocin HCl

brand of clindamycin hydrochloride capsules, USP

Table 2. *(continued)*

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in mcg/mL)	Disk Diffusion (Zone Diameters in mm)
When Testing Strict Anaerobes		
Bacteroides fragilis ATCC 25285	0.5–2	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8	NA
Eubacterium lentum ATCC 43055	0.06–0.25	NA

NA=Not applicable

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

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

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

ATCC® is a registered trademark of the American Type Culture Collection

INDICATIONS AND USAGE

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

Clindamycin 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 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 (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft tissue infections.

Staphylococci: Serious respiratory tract infections; serious skin and soft tissue infections.

Pneumococci: Serious respiratory tract infections.

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

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

CONTRAINDICATIONS

CLEOCIN HCl 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.

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

CLEOCIN HCl should be prescribed with caution in atopic individuals.

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

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

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.

The 75 mg and 150 mg capsules contain FD&C yellow no. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C yellow no. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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

Information for Patients

Patients should be counseled that antibacterial drugs including CLEOCIN HCl should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CLEOCIN HCl is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CLEOCIN HCl or other antibacterial drugs in the future.

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, these 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 1.6 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 (3.2 and 1.6 times the highest recommended adult human dose based on mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (1.3 and 0.7 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.

Pediatric Use

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

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: Abdominal pain, pseudomembranous colitis, esophagitis, nausea, vomiting and diarrhea (see **WARNING** box). The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see **WARNINGS**).

Hypersensitivity Reactions: Generalized mild to moderate morbilliform-like (maculopapular) skin rashes are the most frequently reported adverse reactions. Vesiculobullous rashes, as well as urticaria, have been observed during drug therapy. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, and a few cases of anaphylactoid reactions have also been reported.

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.

Musculoskeletal: Rare instances of polyarthritis have been reported.

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

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

Adults: *Serious infections*—150 to 300 mg every 6 hours. *More severe infections*—300 to 450 mg every 6 hours. **Pediatric Patients:** *Serious infections*—8 to 16 mg/kg/day (4 to 8 mg/lb/day) divided into three or four equal doses. *More severe infections*—16 to 20 mg/kg/day (8 to 10 mg/lb/day) divided into three or four equal doses.

To avoid the possibility of esophageal irritation, CLEOCIN HCl Capsules should be taken with a full glass of water.

Serious infections due to anaerobic bacteria are usually treated with CLEOCIN PHOSPHATE® Sterile Solution. However, in clinically appropriate circumstances, the physician may elect to initiate treatment or continue treatment with CLEOCIN HCl Capsules.

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

HOW SUPPLIED

CLEOCIN HCl Capsules are available in the following strengths, colors and sizes:

75 mg Green	
Bottles of 100	NDC 0009-0331-02
150 mg Light Blue and Green	
Bottles of 16	NDC 0009-0225-01
Bottles of 100	NDC 0009-0225-02
Unit dose package of 100	NDC 0009-0225-03
300 mg Light Blue	
Bottles of 16	NDC 0009-0395-13
Bottles of 100	NDC 0009-0395-14
Unit dose package of 100	NDC 0009-0395-02

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

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 1.6 and 5.4 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 3.2 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 10.8 times the highest recommended adult human dose based on mg/m^2) vomited, would not eat, and lost weight.

℞ only

REFERENCES

1. NCCLS. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-5th ed. NCCLS document M7-A5, 2000. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
2. NCCLS. Performance Standards for Antimicrobial Susceptibility Testing: 13th Informational Supplement. NCCLS document M100-S13 (M2 & M7), 2003. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
3. NCCLS. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria 5th ed. Approved Standard. NCCLS document M11-A5, 2001. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
4. NCCLS. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard-8th ed. NCCLS document M2-A8 (ISBN 1-56238-393-0), 2003. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.

Made in Canada for
Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA
By Patheon YM, Inc., Toronto, Ontario
M3B 1Y5 Canada

Revised November 2003 810 570 928
692851

Pfizer

Composition Unit 2566

Black

COMPOSITION ORDER #	PRODUCT		COPY CODE #
22685	CLEOCIN HCL		810 570 928
CCS #	NDC #	EDP #	ITEM
0225-01	0009-0225-01	692851	Insert
BOTTLE #	SIZE	FOLDED SIZE	DRAWING #
	10 x 10"	2.5 x 1"	PD2364
ADDITIONAL INFORMATION		DATE	TYPESET BY
spine 4" from bottom		12/09/03	KL/DHUFF

Cleocin Phosphate®

clindamycin injection, USP and
clindamycin injection in
5% dextrose

PHARMACIA

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

Sterile Solution is for Intramuscular and Intravenous Use
CLEOCIN PHOSPHATE in the ADD-Vantage™ Vial is 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 non-bacterial 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.

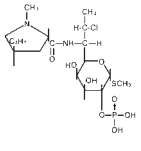
DESCRIPTION

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.

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) 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 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 (61-79 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.

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	
Pediatric Patients (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: Clindamycin inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It has activity against Gram-positive aerobes and anaerobes as well as the Gram-negative anaerobes. Clindamycin is bacteriostatic. Cross-resistance between clindamycin and lincomycin is complete. Antagonism *in vitro* has been demonstrated between clindamycin and erythromycin.

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

Gram-positive aerobes
Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Anaerobes
Prevotella melaninogenica
Fusobacterium necrophorum
Fusobacterium nucleatum
Peptostreptococcus anaerobius
Clostridium perfringens

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for clindamycin. However, the safety and effectiveness of clindamycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive aerobes
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus oralis
Streptococcus mitis

Anaerobes
Prevotella intermedia
Prevotella bivia
Propionibacterium acnes
Micromonas ("Peptostreptococcus") micros
Finegoldia ("Peptostreptococcus") magna
Actinomyces israelii
Clostridium clostridioforme
Eubacterium lentum

SUSCEPTIBILITY TESTING METHODS:

NOTE: Susceptibility testing by dilution methods requires the use of clindamycin susceptibility powder.

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth and agar)[1,2,3] or equivalent with standardized inoculum concentrations and standardized concentrations of clindamycin powder. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques: Quantitative methods that require the measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 2 mcg of clindamycin to test the susceptibility of microorganisms to clindamycin. The disk diffusion interpretive criteria are provided in Table 2.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard clindamycin powder should provide the following range of values noted in Table 3. **NOTE:** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Cleocin Phosphate
brand of clindamycin injection, USP and clindamycin injection in 5% dextrose

Table 2. Susceptibility Interpretive Criteria for Clindamycin

Pathogen	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in mcg/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Staphylococcus spp.	≤0.5	1-2	≥4	≥21	15-20	≤14
Streptococcus pneumoniae and other *Streptococcus* spp.	≤0.25[a]	0.5	≥1	≥19[b]	16-18	≤15
Anaerobic Bacteria[c]	≤2	4	≥8	NA	NA	NA

[a] These interpretive standards for *S. pneumoniae* and other *Streptococcus* spp. are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

[b] These zone diameter interpretive standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20 to 24 hours.

[c] These interpretive criteria are for all anaerobic bacterial pathogens; no organism specific interpretive criteria are available. NA=not applicable

Table 3. Acceptable Quality Control Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in mcg/mL)	Disk Diffusion (Zone Diameters in mm)
When Testing Aerobic Pathogens		
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619[d]	0.03–0.12[e]	19–25[f]
When Testing Strict Anaerobes		
Bacteroides fragilis ATCC 25285	0.5–2	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8	NA
Eubacterium lentum ATCC 43055	0.06–0.25	NA

NA=Not applicable

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

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

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

ATCC® is a registered trademark of the American Type Culture Collection

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.

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.

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

CONTRAINDICATIONS

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

Cleocin Phosphate clindamycin injection, USP and clindamycin IV solution

0810020241

Cleocin Phosphate clindamycin injection, USP and clindamycin IV solution

SPINE

Pfizer

Composition Unit 2566

Black

COMPOSITION ORDER #	PRODUCT		COPY CODE #
23229	CLEOCIN PHOSPHATE		810 020 241B
CCS # 0775-26	NDC # 0009-0775-26	EDP # 692843	ITEM Insert
BOTTLE # x	SIZE 12 x 12"	FOLDED SIZE 3 x 2"	DRAWING # PD2355 R2
ADDITIONAL INFORMATION Spine 4" from top		DATE 1-8-04	TYPESET BY KL

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.

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

Information for Patients

Patients should be counseled that antibacterial drugs including CLEOCIN PHOSPHATE should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CLEOCIN PHOSPHATE is prescribed to treat a bacterial infection, patients should be told that although it is common to

feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CLEOCIN PHOSPHATE or other antibacterial drugs in the future.

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 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 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.

Cleocin Phosphate
brand of clindamycin injection, USP and clindamycin injection in 5% dextrose

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

DOSAGE AND ADMINISTRATION

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

Adults: Parenteral (IM or IV Administration)

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

More severe infections: 1200-2700 mg/day in 2, 3 or 4 equal doses.

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, pediatric patients 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

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 demonstrated physical and chemical stability for at least eight weeks at -10°C.

Frozen solutions should be thawed at room temperature and not refrozen.

DIRECTIONS 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

Cleocin Phosphate
brand of clindamycin injection, USP and clindamycin injection in 5% dextrose

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 0009-0870-26
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 is supplied in ADD-Vantage vials as follows:

NDC	Vial Size	Total Clindamycin Phosphate/vial	Amount of Diluent
0009-3124-03	25-4 mL vials	600 mg	50 mL
0009-3447-03	25-6 mL vials	900 mg	100 mL

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

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 0009-3381-02
24-600 mg/50 mL containers	NDC 0009-3375-02
24-900 mg/50 mL containers	NDC 0009-3382-02

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.

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.

℞ only

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

810 020 241B
692843
0775-26

Revised October 2003

REFERENCES

1. NCCLS. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-5th ed. NCCLS document M7-A5, 2000. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
2. NCCLS. Performance Standards for Antimicrobial Susceptibility Testing: 13th Informational Supplement. NCCLS document M100-S13 (M2 & M7), 2003. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
3. NCCLS. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria 5th ed. Approved Standard. NCCLS document M11-A5, 2001. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
4. NCCLS. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard-8th ed. NCCLS document M2-A8 (ISBN 1-56238-393-0), 2003. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.

‡ 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.

Pfizer

Black

Composition Unit 2566

COMPOSITION ORDER #	PRODUCT		COPY CODE #
23229	CLEOCIN PHOSPHATE		810 020 241B
CCS #	NDC #	EDP #	ITEM
0775-26	0009-0775-26	692843	Insert
BOTTLE #	SIZE	FOLDED SIZE	DRAWING #
x	12 x 12"	3 x 2"	PD2355 R2
ADDITIONAL INFORMATION		DATE	TYPESET BY
Spine 4" from top		1-8-04	KL

Cleocin Phosphate®

clindamycin injection, USP and
clindamycin injection in
5% dextrose

PHARMACIA

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

Sterile Solution is for Intramuscular and Intravenous Use
CLEOCIN PHOSPHATE in the ADD-Vantage™ Vial is 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 non-bacterial 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.

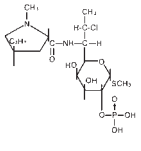
DESCRIPTION

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.

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) 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 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 (61-79 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.

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	
Pediatric Patients (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: Clindamycin inhibits bacterial protein synthesis by binding to the 50S subunit of the ribosome. It has activity against Gram-positive aerobes and anaerobes as well as the Gram-negative anaerobes. Clindamycin is bacteriostatic. Cross-resistance between clindamycin and lincomycin is complete. Antagonism *in vitro* has been demonstrated between clindamycin and erythromycin.

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

Gram-positive aerobes
Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Anaerobes
Prevotella melaninogenica
Fusobacterium necrophorum
Fusobacterium nucleatum
Peptostreptococcus anaerobius
Clostridium perfringens

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for clindamycin. However, the safety and effectiveness of clindamycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Gram-positive aerobes
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus oralis
Streptococcus mitis

Anaerobes
Prevotella intermedia
Prevotella bivia
Propionibacterium acnes
Micromonas ("Peptostreptococcus") micros
Finegoldia ("Peptostreptococcus") magna
Actinomyces israelii
Clostridium clostridioforme
Eubacterium lentum

SUSCEPTIBILITY TESTING METHODS:

NOTE: Susceptibility testing by dilution methods requires the use of clindamycin susceptibility powder.

When available, the results of *in vitro* susceptibility tests should be provided to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth and agar)[1,2,3] or equivalent with standardized inoculum concentrations and standardized concentrations of clindamycin powder. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques: Quantitative methods that require the measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 2 mcg of clindamycin to test the susceptibility of microorganisms to clindamycin. The disk diffusion interpretive criteria are provided in Table 2.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard clindamycin powder should provide the following range of values noted in Table 3. **NOTE:** Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Cleocin Phosphate
brand of clindamycin injection, USP and clindamycin injection in 5% dextrose

Table 2. Susceptibility Interpretive Criteria for Clindamycin

Pathogen	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in mcg/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Staphylococcus spp.	≤0.5	1-2	≥4	≥21	15-20	≤14
Streptococcus pneumoniae and other *Streptococcus* spp.	≤0.25[a]	0.5	≥1	≥19[b]	16-18	≤15
Anaerobic Bacteria[c]	≤2	4	≥8	NA	NA	NA

[a] These interpretive standards for *S. pneumoniae* and other *Streptococcus* spp. are applicable only to tests performed by broth microdilution using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood inoculated with a direct colony suspension and incubated in ambient air at 35°C for 20 to 24 hours.

[b] These zone diameter interpretive standards are applicable only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood inoculated with a direct colony suspension and incubated in 5% CO_2 at 35°C for 20 to 24 hours.

[c] These interpretive criteria are for all anaerobic bacterial pathogens; no organism specific interpretive criteria are available. NA=not applicable

Table 3. Acceptable Quality Control Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	Acceptable Quality Control Ranges	
	Minimum Inhibitory Concentration (MIC in mcg/mL)	Disk Diffusion (Zone Diameters in mm)
When Testing Aerobic Pathogens		
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619[d]	0.03–0.12[e]	19–25[f]
When Testing Strict Anaerobes		
Bacteroides fragilis ATCC 25285	0.5–2	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8	NA
Eubacterium lentum ATCC 43055	0.06–0.25	NA

NA=Not applicable

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

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

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

ATCC® is a registered trademark of the American Type Culture Collection

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.

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.

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

CONTRAINDICATIONS

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

Cleocin Phosphate clindamycin injection, USP and clindamycin IV solution

0810020241

Cleocin Phosphate clindamycin injection, USP and clindamycin IV solution

SPINE

Pfizer

Composition Unit 2566

Black

COMPOSITION ORDER #	PRODUCT		COPY CODE #
23229	CLEOCIN PHOSPHATE		810 020 241B
CCS # 0775-26	NDC # 0009-0775-26	EDP # 692843	ITEM Insert
BOTTLE # x	SIZE 12 x 12"	FOLDED SIZE 3 x 2"	DRAWING # PD2355 R2
ADDITIONAL INFORMATION Spine 4" from top		DATE 1-8-04	TYPESET BY KL

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.

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

Information for Patients

Patients should be counseled that antibacterial drugs including CLEOCIN PHOSPHATE should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CLEOCIN PHOSPHATE is prescribed to treat a bacterial infection, patients should be told that although it is common to

feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CLEOCIN PHOSPHATE or other antibacterial drugs in the future.

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 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 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.

Cleocin Phosphate
brand of clindamycin injection, USP and clindamycin injection in 5% dextrose

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

DOSAGE AND ADMINISTRATION

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

Adults: Parenteral (IM or IV Administration)

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

More severe infections: 1200-2700 mg/day in 2, 3 or 4 equal doses.

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, pediatric patients 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

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 demonstrated physical and chemical stability for at least eight weeks at -10°C.

Frozen solutions should be thawed at room temperature and not refrozen.

DIRECTIONS 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

Cleocin Phosphate
brand of clindamycin injection, USP and clindamycin injection in 5% dextrose

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 0009-0870-26
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 is supplied in ADD-Vantage vials as follows:

NDC	Vial Size	Total Clindamycin Phosphate/vial	Amount of Diluent
0009-3124-03	25-4 mL vials	600 mg	50 mL
0009-3447-03	25-6 mL vials	900 mg	100 mL

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

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 0009-3381-02
24-600 mg/50 mL containers	NDC 0009-3375-02
24-900 mg/50 mL containers	NDC 0009-3382-02

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.

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.

℞ only

Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

810 020 241B
692843
0775-26

Revised October 2003

REFERENCES

1. NCCLS. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-5th ed. NCCLS document M7-A5, 2000. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
2. NCCLS. Performance Standards for Antimicrobial Susceptibility Testing: 13th Informational Supplement. NCCLS document M100-S13 (M2 & M7), 2003. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
3. NCCLS. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria 5th ed. Approved Standard. NCCLS document M11-A5, 2001. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.
4. NCCLS. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard-8th ed. NCCLS document M2-A8 (ISBN 1-56238-393-0), 2003. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898.

‡ 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.

Pfizer

Black

Composition Unit 2566

COMPOSITION ORDER #	PRODUCT		COPY CODE #
23229	CLEOCIN PHOSPHATE		810 020 241B
CCS #	NDC #	EDP #	ITEM
0775-26	0009-0775-26	692843	Insert
BOTTLE #	SIZE	FOLDED SIZE	DRAWING #
x	12 x 12"	3 x 2"	PD2355 R2
ADDITIONAL INFORMATION		DATE	TYPESET BY
Spine 4" from top		1-8-04	KL