

CLEOCIN HYDROCHLORIDE - clindamycin hydrochloride capsule

Pharmacia and Upjohn Company

Cleocin HCl[®] clindamycin
hydrochloride capsules,
USP

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.

WARNING

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CLEOCIN HCL and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C.difficile*.

Because CLEOCIN HCL 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.

C.difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

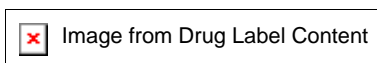
DESCRIPTION

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
Fingoldia ("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
<i>Staphylococcus</i> spp.	≤ 0.5	1–2	≥4	≥21	15–20	≤14
<i>Streptococcus pneumoniae</i> and other <i>Streptococcus</i> spp.	≤0.25*	0.5	≥1	≥19†	16–18	≤15
Anaerobic Bacteria‡	≤2	4	≥8	NA	NA	NA

NA=not applicable

* 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.

† 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% CO₂ at 35°C for 20 to 24 hours.

‡ These interpretive criteria are for all anaerobic bacterial pathogens; no organism specific interpretive criteria are available.

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)
<i>When Testing Aerobic Pathogens</i>		
<i>Staphylococcus aureus</i> ATCC 29213	0.06–0.25	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	24–30
<i>Streptococcus pneumoniae</i> ATCC 49619*	0.03–0.12 [†]	19–25 [‡]
<i>When Testing Strict Anaerobes</i>		
<i>Bacteroides fragilis</i> ATCC 25285	0.5–2	NA
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	2–8	NA
<i>Eubacterium lentum</i> ATCC 43055	0.06–0.25	NA

NA=Not applicable

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- * This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.
- † 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.
- ‡ 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% CO₂ at 35°C for 20 to 24 hours.

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 tuboovarian 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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CLEOCIN HCl, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. Clostridium difficile*.

C. Clostridium difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated.

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.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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/m²) 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/m², 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/m², 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 polyarthrititis 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/m², 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/m²) 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/m²) vomited, would not eat, and lost weight.

Rx 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.