

Clindamycin HCl

Capsules USP

Revised: June 2003

Rx only

WARNING

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

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

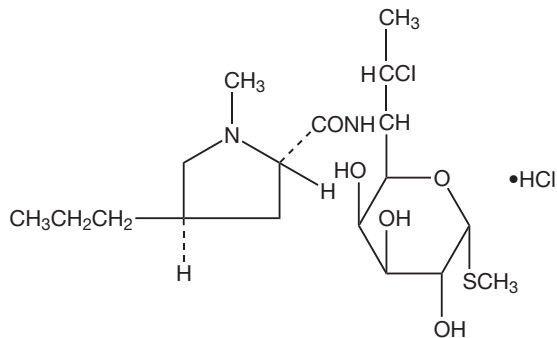
After the diagnosis of pseudo-membranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, 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.

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. The structural formula is represented below:



$C_{18}H_{33}ClN_2O_5S \cdot HCl$

M.W. 461.44

Clindamycin Hydrochloride Capsules USP (equivalent to 150 mg or 300 mg clindamycin) contain the following inactive ingredients: anhydrous lactose, magnesium stearate, starch (corn) and talc. The capsule shells contain: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The 150 mg capsule shell also contains black iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

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

Aerobic gram-positive cocci, including:

Staphylococcus aureus

Staphylococcus epidermidis

(penicillinase and nonpenicillinase producing strains).

When tested by *in vitro* methods some staphylococcal strains originally resistant to erythromycin rapidly develop resistance to clindamycin.

Streptococci (except *Streptococcus faecalis*)

Pneumococci

Anaerobic gram-negative bacilli, including:

Bacteroides species (including *Bacteroides fragilis* group and *Bacteroides melaninogenicus* group)

Fusobacterium species

Anaerobic gram-positive nonsporeforming bacilli, including:

Propionibacterium

Eubacterium

Actinomyces species

Anaerobic and microaerophilic gram-positive cocci, including:

Peptococcus species

Peptostreptococcus species

Microaerophilic streptococci

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

Cross resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

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 clindamycin hydrochloride 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 function¹.

INDICATIONS AND USAGE

Clindamycin hydrochloride capsules are indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin hydrochloride capsules 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 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).

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.

In Vitro Susceptibility Testing: A standardized disk testing procedure* is recommended for determining susceptibility of aerobic bacteria to clindamycin. Using this method, the laboratory can designate isolates as resistant, intermediate, or susceptible. Tube or agar dilution methods may be used for both anaerobic and aerobic bacteria. An MIC of 1.6 mcg/mL may be considered susceptible; MICs of 1.6 to 4.8 mcg/mL may be considered intermediate and MICs greater than 4.8 mcg/mL may be considered resistant.

*Bauer AW, Kirby WMM, Sherris JC, et al: Antibiotic susceptibility testing by a standardized single disc method. *Am J Clin Pathol* **45**:493-496, 1966. Standardized disc susceptibility test, *Federal Register* **37**:20527-29, 1972.

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

CONTRAINDICATIONS

Clindamycin hydrochloride capsules are 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.

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

Clindamycin hydrochloride should be prescribed with caution in atopic individuals.

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

The use of clindamycin hydrochloride 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.

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 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 clindamycin hydrochloride 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 polyarthritides 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, clindamycin hydrochloride capsules should be taken with a full glass of water.

Serious infections due to anaerobic bacteria are usually treated with clindamycin phosphate injection. However, in clinically appropriate circumstances, the physician may elect to initiate treatment or continue treatment with clindamycin hydrochloride capsules.

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

HOW SUPPLIED

Clindamycin Hydrochloride Capsules USP (equivalent to 150 mg of Clindamycin) are opaque gray and opaque pink capsules imprinted "DAN 5708" supplied in bottles of 100.

Clindamycin Hydrochloride Capsules USP (equivalent to 300 mg of Clindamycin) are opaque pink capsules imprinted "DAN 3120" supplied in bottles of 10, 16 and 100.

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 dosage 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 dosage 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.

Dispense in a tight container with a child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

REFERENCES

1. Smith RB, Phillips JP: Evaluation of Clindamycin Hydrochloride and Clindamycin Phosphate in an Aged Population. Upjohn TR 8147-82-9122-021, December 1982.

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