Cleocin Pediatric®

clindamycin palmitate hydrochloride for oral solution, USP

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

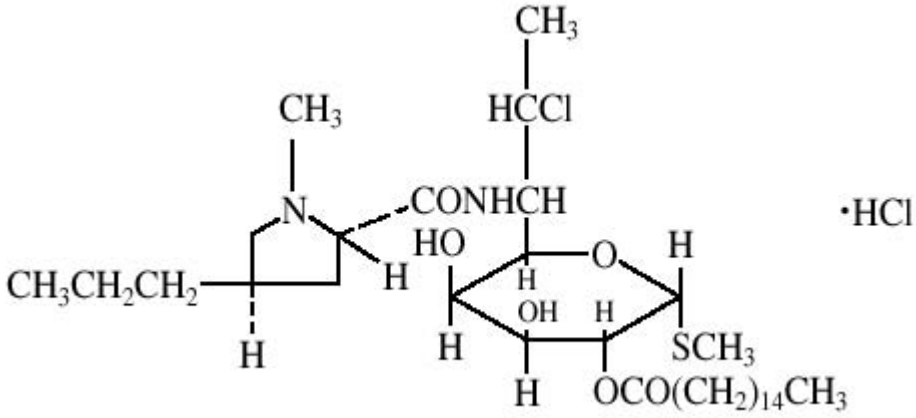
Not for Injection

WARNING *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin 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 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. *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 palmitate hydrochloride is a water soluble hydrochloride salt of the ester of clindamycin and palmitic acid. Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin. The structural formula is represented below:



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The chemical name for clindamycin palmitate 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 2-palmitate monohydrochloride.

CLEOCIN PEDIATRIC Flavored Granules contain clindamycin palmitate hydrochloride for reconstitution. Each 5 mL contains the equivalent of 75 mg clindamycin. Inactive ingredients: artificial cherry flavor, dextrin, ethylparaben, pluronic F68, simethicone, sucrose.

CLINICAL PHARMACOLOGY

Microbiology: Although clindamycin palmitate HCl is inactive *in vitro,* rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

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

Aerobic gram positive cocci, including:

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

Staphylococcus epidermidis

Streptococci (except *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: Blood level studies comparing clindamycin palmitate HCl with clindamycin hydrochloride show that both drugs reach their peak active serum levels at the same time, indicating a rapid hydrolysis of the palmitate to the clindamycin.

Clindamycin is widely distributed in body fluids and tissues (including bones). Approximately 10% of the biological activity is excreted in the urine. The average

serum half-life after doses of CLEOCIN PEDIATRIC is approximately two hours in pediatric patients.

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.

Serum level studies with clindamycin palmitate HCI in normal pediatric patients weighing 50-100 lbs given 2, 3 or 4 mg/kg every 6 hours (8, 12 or 16 mg/kg/day) demonstrated mean peak clindamycin serum levels of 1.24, 2.25 and 2.44 mcg/mL respectively, one hour after the first dose. By the fifth dose, the 6-hour serum concentration had reached equilibrium. Peak serum concentrations after this time would be about 2.46, 2.98 and 3.79 mcg/mL with doses of 8, 12 and 16 mg/kg/day, respectively. Serum levels have been uniform and predictable from person to person and dose to dose. Multiple-dose studies in neonates and infants up to 6 months of age show that the drug does not accumulate in the serum and is excreted rapidly. Serum levels exceed the MICs for most indicated organisms for at least six hours following administration of the usually recommended doses of CLEOCIN PEDIATRIC in adults and pediatric patients.

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; administration of clindamycin palmitate HCl resulted in a similar elimination half-life value of about 4.5 hours in elderly subjects. However, the extent of absorption is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function[1].

INDICATIONS AND USAGE

CLEOCIN PEDIATRIC (clindamycin palmitate HCl) 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 (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[2] is recommended for determining susceptibility of aerobic bacteria to clindamycin. A description is contained in the CLEOCIN® Susceptibility Disk (clindamycin) insert. 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. When the directions in the CLEOCIN® Susceptibility Powder insert are followed, an MIC (minimal inhibitory concentration) 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. CLEOCIN Susceptibility Disks 2 mcg. See package insert for use. CLEOCIN Susceptibility Powder 20 mg. See package insert for use.

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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CLEOCIN PEDIATRIC and other antibacterial drugs, CLEOCIN PEDIATRIC 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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CLEOCIN PEDIATRIC (Clindamycin Palmitate 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*.

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.

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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 PEDIATRIC (clindamycin palmitate HCI) should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

CLEOCIN PEDIATRIC should be prescribed with caution in atopic individuals.

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

The use of CLEOCIN PEDIATRIC 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.

Prescribing CLEOCIN PEDIATRIC 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 PEDIATRIC should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CLEOCIN PEDIATRIC 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 PEDIATRIC 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 oral 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 oral 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 oral 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 HCI 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 subjects (18-39 years) and elderly subjects (61-79 years) 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).

Concomitant administration of food does not adversely affect the absorption of clindamycin palmitate HCl contained in CLEOCIN PEDIATRIC Flavored Granules.

Serious infections: 8-12 mg/kg/day (4-6 mg/lb/day) divided into 3 or 4 equal doses.

Severe infections: 13-16 mg/kg/day (6.5-8 mg/lb/day) divided into 3 or 4 equal doses.

More severe infections: 17-25 mg/kg/day (8.5-12.5 mg/lb/day) divided into 3 or 4 equal doses.

In pediatric patients weighing 10 kg or less, ½ teaspoon (37.5 mg) three times a day should be considered the minimum recommended dose.

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 PEDIATRIC.

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

Reconstitution Instructions: When reconstituted with water as follows, each 5 mL (teaspoon) of solution contains clindamycin palmitate HCl equivalent to 75 mg clindamycin.

Reconstitute bottles of 100 mL with **75 mL** of water. Add a large portion of the water and shake vigorously; add the remainder of the water and shake until the solution is uniform.

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

Do **NOT** refrigerate the reconstituted solution; when chilled, the solution may thicken and be difficult to pour. The solution is stable for 2 weeks at room temperature.

HOW SUPPLIED

CLEOCIN PEDIATRIC Flavored Granules for oral solution is available in bottles of 100 mL (NDC 0009-0760-04).

When reconstituted as directed, each bottle yields a solution containing 75 mg of clindamycin per 5 mL.

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 oral 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 oral 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 oral dose based on mg/m^2) vomited, would not eat, and lost weight.

Rx only

References

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

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