

DALACIN[®] C PHOSPHATE

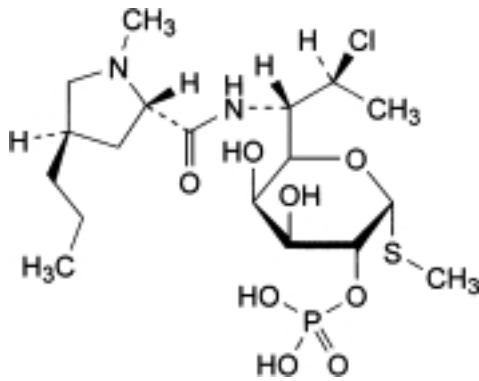
Clindamycin Injection

For Intramuscular and Intravenous Use

DESCRIPTION

DALACIN C Phosphate (clindamycin- phosphate injection) is a sterile solution of a water soluble ester of clindamycin and phosphoric acid which contains the equivalent of 150 mg clindamycin base, 9.45 mg benzyl alcohol and 0.5 mg disodium edetate in each mL of water for injection. Clindamycin is a semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

The MW of clindamycin-2-phosphate is 504.96 and its structural formula is represented below:



ACTION

Microbiology

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

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

Aerobic gram-positive cocci, including:

Staphylococcus aureus

Staphylococcus epidermidis (penicillinase and non-penicillinase producing strains).

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

Streptococci (not *Enterococcus faecalis*)

Pneumococci

Anaerobic gram-negative bacilli, including:

Bacteroides species

Fusobacterium species

Anaerobic gram-positive non-spore forming 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 *C. perfringens* are susceptible, but other species, e.g., *C. sporogenes* and *C. tertium* are frequently resistant to clindamycin.

Susceptibility testing should be done.

Cross-resistance has been demonstrated between clindamycin and lincomycin.

Disc Susceptibility Testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility testing procedures require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures.

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, which 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 and other therapy should be selected.

The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

HUMAN 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 disappearance half-life is 6 minutes; however, the serum disappearance half-life of active clindamycin is about 3 hours in adults and 2.5 hours in children.

After intramuscular injection of DALACIN C Phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in children. Serum level curves may be

constructed from IV peak serum levels as given in Table 1 by application of the disappearance 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 DALACIN C Phosphate every 8-12 hours in adults and every 6-8 hours in children, or by continuous intravenous infusion. An equilibrium state is reached by the third dose.

The disappearance half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function; dosage schedules need not be modified in the presence of mild to moderate renal or hepatic disease. No significant levels of clindamycin are attained in the cerebrospinal fluid even in the presence of inflamed meninges.

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

Table 1: Average Peak Serum Concentrations After Dosing with DALACIN® C Phosphate

Dosage Regimen	Clindamycin (micrograms/mL)	Clindamycin Phosphate (micrograms/mL)
Healthy Adult Males (Post Equilibrium)		
300 mg IV in 10 min q 8h	7	15
600 mg IV in 20 min q 8h	10	23
900 mg IV in 30 min q 12h	11	29
1200 mg IV in 45 min q 12h	14	49
300 mg IM q 8h	6	3
600 mg IM q 12h*	9	3
Children (first dose)*		
5-7 mg/kg in 1 h	10	
3-5 mg/kg IM	4	
5-7 mg/kg IM	8	

*Data in this group from patients being treated for infection

INDICATIONS

Clindamycin phosphate has been shown to be effective in the treatment of the following infections when caused by susceptible anaerobic bacteria or susceptible strains of gram positive bacteria such as streptococci, staphylococci and pneumococci:

1. Upper respiratory infections including tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever.
2. Lower respiratory infections including bronchitis, pneumonia, emphyema and lung abscess.
3. Skin and soft tissue infections including acne, furuncles, cellulitis, impetigo, abscesses, and wound infections. For specific skin and soft tissue infections like erysipelas and paronychia (panaritium), it would seem logical that these conditions would respond very well to clindamycin therapy.
4. Bone and joint infections including osteomyelitis and septic arthritis.
5. Pelvic infections including endometritis, cellulitis, vaginal cuff infection tubo-ovarian abscesses salpingitis and pelvic inflammatory disease when given in conjunction with an antibiotic of appropriate gram negative aerobic spectrum. In cases of cervicitis due to *Chlamydia trachomatis*, mono therapy with clindamycin has been shown to be effective in eradicating the organism.
6. Intra-abdominal infections including peritonitis and abdominal abscess when given in conjunction with an antibiotic of appropriate gram negative aerobic spectrum.
7. Septicemia and endocarditis - the effectiveness of clindamycin in the treatment of selected cases of endocarditis has been documented when clindamycin is determined to be bactericidal to the infecting organism by *in vitro* testing of appropriate achievable serum concentrations.
8. Dental infections such as periodontal abscess and periodonitis.
9. Toxoplasmic encephalitis in patients with AIDS. In patients who are intolerant to conventional treatment, clindamycin in combination with pyrimethamine has been shown to be efficacious.
10. *Pneumocystis carinii* pneumonia in patients with AIDS. In patients who are intolerant to or do not respond to conventional treatment, clindamycin in combination with primaquine has been shown to be efficacious.

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin or any of the ingredients listed under ‘Description’.

PRECAUTIONS

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

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

The use of clindamycin can lead to the development of severe colitis. Fatalities have been reported. Therefore, DALACIN C Phosphate should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS section. It should not be used in patients with non-bacterial infections such as most upper respiratory tract infections.

A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with the use of antibiotics, including parenteral clindamycin. Symptoms may occur up to several weeks after cessation of antibiotic therapy. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*. The colitis is usually characterized by mild watery diarrhoea to severe, persistent diarrhoea, leukocytosis, fever, severe abdominal cramps which may be associated with the passage of blood and mucous and if allowed to progress may produce peritonitis, shock and toxic megacolon. Endoscopic examination may reveal pseudomembranous colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone, however in moderate to severe cases appropriate therapy with suitable oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

When significant diarrhoea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large bowel endoscopy has been recommended.

Vancomycin has been found to be effective in the treatment of antibiotic associated pseudomembranous colitis produced by *Clostridium difficile*. The usual adult dose is 500 mg to 2 g of vancomycin orally per day in three to four divided doses administered for seven to ten days.

If both a resin and vancomycin are to be administered con-currently, it may be advisable to separate the time of administration of each drug.

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

Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

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

Antibiotic-associated colitis and diarrhoea (due to *C. difficile*), occur more frequently and may be more severe in debilitated and/or elderly patients (> 60 years). When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhoea 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

DALACIN C Phosphate should be prescribed with caution in atopic individuals.

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

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe, metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy. The use of DALACIN C Phosphate may result in overgrowth of nonsusceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

DALACIN C 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.

Drugs which delay peristalsis (*e.g.*, opiates and diphenoxylate with atropine [Lomotil LOMOTIL[®]]) may prolong and/or worsen the condition and should not be used.

DALACIN C Phosphate should be used with caution in patients with a history of regional enteritis, ulcerative colitis or antibiotic associated colitis.

Stool culture for *Clostridium difficile* and stool assay for *C. difficile* toxin maybe helpful diagnostically.

Use in Pregnancy: Category A

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal concentrations. Clindamycin should be used in pregnancy only if clearly needed.

Usage in the Newborn and Infants

When DALACIN C Phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Use in Lactation

Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 micrograms/mL, therefore, it is not recommended for nursing mothers.

Usage in Meningitis

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

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 DALACIN C Phosphate and erythromycin *in vitro*. Because of possible clinical significance these two drugs should not administered concurrently (see "Compatibility / Incompatibility" for physicochemical interactions).

ADVERSE REACTIONS

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

Gastrointestinal

Abdominal pain, nausea, vomiting and diarrhoea (see "Precautions").

Hypersensitivity Reactions

Maculopapular rash and urticaria have been observed during drug therapy. Generalised 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 (adrenaline, corticosteroids, colloid infusion, antihistamines) should be available for emergency treatment of serious reactions.

Liver

Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Skin and Mucous Membranes

Pruritis, skin rashes, urticaria, vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported.

Rare cases of toxic epidermal necrolysis have been reported during post-marketing surveillance.

Haemopoietic

Transient neutropenia (leucopenia) and eosinophilia have been reported. Rare cases of agranulocytosis and thrombocytopenia have been reported. No direct cause/effect relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Cardiovascular

Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. (see “Dosage and Administration”).

Musculoskeletal

Rare instances of polyarthritis have been reported.

Nervous System

Dysgeusia.

Local Reactions

Local irritation, pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimised by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

DOSAGE AND ADMINISTRATION

If significant diarrhoea occurs during therapy, this antibiotic should be discontinued (see “Precautions”).

Adults: Serious Infections: 150 mg – 300 mg every six hours.

 More severe infections: 300 mg – 450 mg every six hours.

Children: Serious Infections: 8 – 16 mg/kg/day divided into three or four equal doses.

 More severe infections: 16 – 25 mg/kg/day divided into three or four equal doses.

For the treatment of Pelvic Inflammatory Disease - Inpatient treatment

Clindamycin phosphate 900 mg (IV) q8h daily plus an antibiotic with an appropriate gram negative aerobic spectrum administered IV; e.g. gentamicin 2.0 mg/kg followed by 1.5 mg/kg q8h daily in patients with normal renal function. Continue (IV) drugs for at least 4 days and at least 48 hours after the patient improves. Then continue oral clindamycin hydrochloride 450 mg q6h daily to complete 10-14 days total therapy.

For the treatment of Cervicitis Due to *Chlamydia trachomatis*:

Clindamycin hydrochloride by mouth 450mg 4 times daily for 10-14 days.

For the treatment of β -hemolytic streptococci infections

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

For the treatment of Toxoplasmic encephalitis in patients with AIDS

Clindamycin phosphate IV or clindamycin hydrochloride by mouth 600-1200 mg every 6 hours for two weeks followed by 300-600 mg by mouth every 6 hours. The usual total duration of therapy is 8 to 10 weeks. The dose of pyrimethamine is 25-75 mg by mouth daily for 8-10 weeks. Folinic acid 10-20 mg/day should be given with higher doses of pyrimethamine.

For the treatment of *Pneumocystis carinii* pneumonia in patients with AIDS

Clindamycin phosphate IV 600-900 mg every 6 hours or 900 mg IV every 8 hours or clindamycin hydrochloride 300-450 mg by mouth every 6 hours for 21 days. Primaquine 15-30 mg dose by mouth once daily for 21 days.

Dilution and Infusion Rates

DALACIN C Phosphate must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL AND INFUSED AT A RATE OF NOT MORE THAN 30 MG PER MINUTE AS INDICATED BELOW:

Table 2: Dilution and Infusion Rates in Relation to Total Infusion Dose

Dose	Diluent	Minimum 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.

DIRECTIONS FOR USE

The neck of the ampoule is pre-scored at the point of constriction. (No ampoule file is needed to open the ampoules.) A coloured dot on the ampoule head helps to orientate the ampoule. Take the ampoule and face the coloured dot. The ampoule opens easily by placing the thumb on the coloured dot and gently pressing downwards.

COMPATIBILITY / INCOMPATIBILITY

DALACIN C Phosphate has been known to be physically and chemically compatible for at least 24 hours in glucose 5% water and sodium chloride injection solutions containing the following antibiotics in usually administered concentrations:

amikacin sulfate, aztreonam, cephmandole nafate, cefazolin sodium, cefotaxime sodium, ceftazidime sodium, ceftizoxime sodium, gentamicin sulfate, netilmicin sulfate, piperacillin and tobramycin.

The compatibility and duration of stability of drug mixtures will vary depending on concentration and other conditions.

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

The following drugs are physically incompatible with DALACIN C Phosphate:

ampicillin, phenytoin sodium, barbiturates, aminophylline, calcium gluconate, magnesium sulphate, ceftriaxone sodium and ciprofloxacin.

OVERDOSAGE

The minimal toxic or lethal dose is not well established. At therapeutic doses, the primary toxic effects may involve the gastrointestinal tract and may include severe diarrhoea and pseudomembranous colitis that may result in death. Rapid administration of large doses has resulted in ventricular dysrhythmias, hypotension and cardiac arrest. Dermatitis, nephrotoxicity, hepatotoxicity, and various haematological abnormalities are toxic effects that occur less frequently.

No specific antidote is known. Support respiratory and cardiac function. In cases of overdose, drug levels of clindamycin are not clinically useful. However, monitoring serum concentrations in patients with markedly reduced renal and hepatic function, may be indicated during high-dose therapy. Monitor full blood count in patients with significant exposure as clindamycin may produce abnormalities of the haematopoietic system. Because clindamycin may cause hepatotoxicity, monitor liver function tests in patients with significant exposure.

Neither haemodialysis nor peritoneal dialysis appear to be effective in reducing clindamycin levels significantly.

Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen and intravenous corticosteroids should also be administered as indicated.

Contact the National Poisons Centre for advice on the management of an overdose.

PRESENTATIONS

Each 1 mL of DALACIN C Phosphate contains clindamycin phosphate equivalent to 150 mg clindamycin base; 9.45 mg benzyl alcohol; 0.5 mg disodium edetate; and Water for Injections q.s.. When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid.

The following sizes are available:

4 mL ampoule (600 mg) - 1's

Also available for oral administration:

DALACIN C Capsules 150 mg - Each capsule contains clindamycin hydrochloride hydrate equivalent to 150 mg clindamycin base.

Please consult prescribing information on oral formulations for further details.

NAME AND ADDRESS OF SPONSOR

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