WARNING
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Clindamycin Injection, USP 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 antibacterials 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 intervention should be instituted as clinically indicated.

DESCRIPTION:
Clindamycin Injection, USP for intramuscular and intravenous use, a water soluble ester of clindamycin and phosphoric acid. Each mL contains clindamycin phosphate equivalent to 150 mg clindamycin, 0.5 mg disodium edetate and 9.45 mg benzyl alcohol added as preservative. When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid. Clindamycin is a semi-synthetic antibiotic produced by a 7-(2-chloro substituted of the 7(R)-hydroxy group of the parent compound lincomycin.

The chemical name of clindamycin phosphate is L-threo–D-galacto-Octopyranoside, methyl 7-chloro-6,7 dihydroxy-6-[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]alpha-1-thio, 2-(dihydrogen phosphate), (25-trans). The structural formula is represented below:

\[
\text{C}_{14}\text{H}_{21}\text{Cl}\text{NiO}_{6}\text{PhS}
\]

M.W. 504.97

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. Table 1 by application of elimination half-lives listed above.

Serum levels of clindamycin can be maintained above the in vitro minimal inhibitory concentration 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 to 79 years) and younger adults (18 to 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 hours (range 3.4 to 5.1 h) in the elderly compared to 3.2 hours (range 2.1 to 4.2 h) in younger adults. The extent of absorption, however, is not different between age groups and no dose reduction 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

<table>
<thead>
<tr>
<th>Dosage Regimen</th>
<th>Peak mcg/mL</th>
<th>Trough mcg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Adult Dose (Post equilibrium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600 mg IV in 30 min q8h</td>
<td>10.9</td>
<td>2</td>
</tr>
<tr>
<td>600 mg IV in 30 min q12h</td>
<td>10.8</td>
<td>1.1</td>
</tr>
<tr>
<td>900 mg IV in 30 min q12h</td>
<td>14</td>
<td>1.7</td>
</tr>
<tr>
<td>600 mg IM (12h)</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Pediatric Patients (first dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 7 mg/kg IV in 1 hour</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>5 to 7 mg/kg IM</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>3 to 5 mg/kg IM</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data in this group from patients being treated for infection.

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 (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 (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 (except Enterococcus faecalis)

- Anaerobic gram negative bacilli, including:
  - Fusobacterium species (including Bacteroides fragilis group and Bacteroides melaninogenicus group)
  - Bacillales 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 sordellii and Clostridium tetani are frequently resistant to clindamycin. Susceptibility testing should be performed.

- Cross-resistance has been demonstrated between clindamycin and lincomycin.

Antagonism has been demonstrated between clindamycin and erythromycin.

In vitro Susceptibility Testing:
Disk diffusion technique—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure\(^1\) has been recommended for use with disks to test susceptibility to clindamycin.

Reports from a laboratory using the standardized single-disk susceptibility test\(^2\) and a 2 mcg clindamycin disk should be interpreted according to the following criteria:

- Susceptible organisms produce zones of 17 mm or greater, indicating that the tested organism is likely to respond to therapy.
- Organisms of intermediate susceptibility produce zones of 15 to 16 mm, indicating that the tested organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.
- Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.

Standardized procedures require the use of control organisms. The 2 mcg clindamycin disk should give a zone diameter between 24 and 30 mm for S. aureus ATCC 29213.

Dilution technique—A bacterial isolate may be considered susceptible if the minimum inhibitory concentration (MIC) for clindamycin is not more than 1.6 mcg/mL. Organisms are considered moderately susceptible if the MIC is greater than 1.6 mcg/mL. For Intramuscular and Intravenous Use

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Clindamycin Injection, USP and other antibacterial drugs, Clindamycin injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.
1.6 mcg/mL and less than or equal to 4.8 mcg/mL. Organisms are considered resistant if the MIC is greater than or equal to 4.8 mcg/mL. The range of MICs for the control strains are as follows:

- S. aureus ATCC 29213, 0.06-0.25 mcg/mL
- E. faecalis ATCC 29212, 4-16 mcg/mL

Bacteria in the minimum 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 use. TheKirby-Bauer DISK DIFFUSION METHOD AND ITS INTERPRETATIVE STANDARDS ARE NOT RECOMMENDED FOR ANAEROBES.

INDICATIONS AND USAGE:
Clindamycin Injection, USP is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

- Clindamycin Injection, USP is also indicated in the treatment of serious infections caused by susceptible bacteria where anaerobes are presumed or known to be present, especially with infections caused by clostridial organisms. In the absence of such data, local epidemiology should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology should be considered in selecting or modifying antibacterial therapy. The use of clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

- Clindamycin should not be injected intravenously undiluted as a bolus. The initial dose should be administered at least 10 to 60 minutes as directed in the DOSAGE AND ADMINISTRATION section. The use of clindamycin injection 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 clindamycin or other antibacterial drugs in the future. Treatment with antibacterial agents alters the normal balance of microorganisms existing in the body. The development of drug-resistant bacteria may occur if an antibacterial is not used in accordance with the recommendations for its use and treatment of infections as described in the PRECAUTIONS, DOSAGE, AND ADMINISTRATION section. Consideration should be given to reporting cases of any unexpected superinfections to the appropriate state department of health and the FDA.

- Clindamycin has been shown to have neuromuscular blocking activity. The use of clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

- Clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

- Clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

- Clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

- Clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

- Clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

- Clindamycin may result in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.
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 diarrhea occurs during therapy, this antibiotic should be discontinued (see **WARNING** box).

**Adults**

Parenteral (IM or IV administration)

Serious infections due to aerobic gram-positive cocci and the more susceptible anaerobes (NOT generally including Bacteroides fragilis, Peptococcus species and Clostridium species other than Clostridium perfringens): 600 to 1200 mg/day in 2, 3 or 4 equal doses.

More severe infections, particularly those due to proven or suspected Bacteroides fragilis, Peptococcus species, or Clostridium species other than Clostridium perfringens: 1200 to 2700 mg/day in 2, 3 or 4 equal doses.

For more serious infections, these doses may have to be increased.

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** 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:

<table>
<thead>
<tr>
<th>Clindamycin levels</th>
<th>Rapid infusion rate</th>
<th>Maintenance infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 4 mcg/mL</td>
<td>10 mg/min</td>
<td>0.75 mg/min</td>
</tr>
<tr>
<td>Above 5 mcg/mL</td>
<td>15 mg/min</td>
<td>1 mg/min</td>
</tr>
<tr>
<td>Above 6 mcg/mL</td>
<td>20 mg/min</td>
<td>1.25 mg/min</td>
</tr>
</tbody>
</table>

**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/m²/day for serious infections and 450 mg/m²/day for more severe infections.

Parenteral therapy may be changed to clindamycin palmitate hydrochloride for oral solution or clindamycin 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 Injection, USP must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 16 mg per mL. Infusion rates should not exceed 30 mg per minute. The usual infusion dilutions and rates are as follows:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Diluent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>50 mL</td>
<td>10 min</td>
</tr>
<tr>
<td>600 mg</td>
<td>50 mL</td>
<td>20 min</td>
</tr>
<tr>
<td>900 mg</td>
<td>50 to 100 mL</td>
<td>30 min</td>
</tr>
<tr>
<td>1200 mg</td>
<td>100 mL</td>
<td>40 min</td>
</tr>
</tbody>
</table>

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 Clindamycin Injection, USP 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 visit [www.APPpharma.com](http://www.APPpharma.com) or call our medical information and safety department toll-free at 1-800-551-7176.

**Physico-Chemical Stability of Diluted Solutions of Clindamycin**

Room temperature: 6, 9 and 12 mg/mL (equivalent to clindamycin base) in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, 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 5% Dextrose Injection, 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 5% Dextrose Injection, 0.9% Sodium Chloride Injection, 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 5% Dextrose Injection, 0.9% Sodium Chloride Injection, 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.

**HOW SUPPLIED:**

Clindamycin Injection, USP supplied as clindamycin phosphate equivalent to clindamycin 150 mg/mL is supplied as follows:

<table>
<thead>
<tr>
<th>Product</th>
<th>NDC No.</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>28202</td>
<td>63323-282-02</td>
<td>2 mL</td>
</tr>
<tr>
<td>28204</td>
<td>63323-282-04</td>
<td>4 mL</td>
</tr>
<tr>
<td>28206</td>
<td>63323-282-06</td>
<td>6 mL</td>
</tr>
</tbody>
</table>

Packaged in twenty-fives.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

**Do not refrigerate.**

Vial stoppers do not contain natural rubber latex.

**ANIMAL TOXICOLOGY:**

One year oral toxicity studies in Spartan Sprague-Dawley rats and beagle dogs at dose levels up to 3000 mg/kg/day (approximately 1.1 and 3.6 times the highest recommended adult human dose based on mg/kg, 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/kg) for six months tolerated the drug well; however, dogs dosed at this level (approximately 7.2 times the highest recommended adult human dose based on mg/kg) vomited, would not eat, and lost weight.

**REFERENCES:**