**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 cldamycin 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. Hyperprolinogucing 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 Injection, USP for intravenous use contains clindamycin phosphate, 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 semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7β-hydroxy group of the parent compound lincomycin.

The chemical name of clindamycin phosphate is L-threo-α-D-galacto-0-caprononic acid, methyl-7-chloro-6,7,8-trideoxy-6-[1-methyl-4-propyl-2-(pyrrolidinyl)[carboxyl] amino]-1-thio- 2 (dihydrogen phosphate), (2S-trans).

The structural formula is represented below:

![Clindamycin Phosphate Structure](image)

**CLINICAL PHARMACOLOGY:**

**Distribution:**

Biologically inactive clindamycin phosphate is converted to active clindamycin. By the end of short-term intravenous infusion, peak serum levels of active clindamycin are reached. Serum level curves may be constructed from IV peak serum levels as given in Table 1 by application of elimination half-lives (see Excretion). Serum levels of clindamycin can be maintained above the in vitro minimum inhibitory concentrations for most isolated 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.

**Excretion:**

Biologically inactive clindamycin phosphate disappears rapidly from 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 6 hours in pediatric patients.

**Special Populations:**

**Renal/Hepatic Impairment:** The elimination half-life of clindamycin is slightly increased 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.

**Use in Elderly:**

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 4.0 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 dosage alteration 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.

**Microbiology:**

**Mechanism of Action:**

Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is bacteriostatic.

**Resistance:**

Resistance to clindamycin is most often caused by modification of specific bases of the 23S ribosomal RNA. Cross-resistance occurs between in vitro and in vivo susceptibility test procedures requiring clindamycin and in vivo data is complete. Because the binding sites for these antibacterials are similar, resistance to one is often observed with the other. Resistance to clindamycin in susceptible strains is sometimes observed among Lincosamides, macrolides and streptogramin B. Macrolide-inducible resistance to clindamycin occurs in some isolates of macrolide-resistant bacteria. Macrolide-resistent isolates of Staphylococci and beta-hemolytic streptococci should be screened for induction of clindamycin resistance using the D-zone test.

**Antimicrobial Activity:**

Clindamycin has been shown to be active against many of the isolates of the following microorganisms, both in vitro and in clinical infections, as described in the INDICATIONS AND USAGE section.

**Gram-positive Bacteria**

Staphylococcus aureus (methicillin-susceptible strains)

Streptococcus pneumoniae (penicillin-susceptible strains)

Streptococcus pyogenes

**Anaerobic Bacteria**

Clostridium perfringens

Fusobacterium necrophorum

Fusobacterium nucleatum

Peptostreptococcus anaerobius

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Clindamycin should be prescribed with caution in patients with a history of seizures. Clindamycin should not be used in patients with known seizures. Clindamycin should not be used as a prophylactic agent in patients with atopic individuals.

**SUSCEPTIBILITY TESTING METHODS**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs) of antibiotics for bacteria and describe the susceptibility of bacteria to antibacterial compounds. The MIC values should be interpreted according to the criteria provided in Table 2.

**Dilution Techniques**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MIC values should be interpreted according to the criteria provided in Table 2.
Benzyl Alcohol Toxicity in Pediatric Patients ("Gasping Syndrome")

Intravenous use should be limited to situations where the potential benefits outweigh the risks. Benzyl alcohol has been associated with adverse reactions, including respiratory distress and anaphylaxis, in neonates and infants. The use of benzyl alcohol in pediatric patients should be considered carefully and justified on a case-by-case basis.

PRECAUTIONS:

General

Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diuretic use less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

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 due to susceptible strains of streptococci, pneumococci, and staphylococci that are susceptible to clindamycin by disk susceptibility tests. In the treatment of streptococcal disease, this drug 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 antibiotic-associated pseudomembranous colitis, as defined in the Important Safety Information, before selecting clindamycin the physician should consider the nature of the infection and the suitability of alternative (e.g., erythromycin).

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Anaerobic bacteria: There may be an interplay between anaerobic and aerobes in the pathogenesis of infections. In cases of mixed infections, anaerobes may play a significant role. Therefore, in serious infections, anaerobic bacteria should be considered as potential pathogens. When appropriate, anaerobic antibiotic therapy should be used in conjunction with clindamycin to attain an adequate peak serum level after the initial dose of clindamycin.

Clindamycin injection, USP is also indicated in the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions listed below.

Intra-abdominal infections including peritonitis and abscesses caused by anaerobes, Streptococcus pneumoniae, other streptococci (except E. faecalis), and Staphylococcus aureus.

Skin and skin structure infections caused by Streptococcus pyogenes, Staphylococcus aureus, and anaerobes.

Gynecological infections including endometritis, nongonococcal pelvic abscess, pelvic cellulitis, and postpartum and postpartum cephtriaffected veterinary unit.

Intra-abdominal infections including peritonitis and intra-abdominal abscesses caused by susceptible anaerobes.

Septicemia caused by Staphylococcus aureus, streptococci (except Enterococcus faecalis), and susceptible anaerobes.

Bone and joint infections including acute hematogenous osteomyelitis caused by Staphylococcus aureus and as adjunctive therapy in the surgical treatment of chronic bone and joint infections due to susceptible anaerobic organisms.

To reduce the development of drug-resistance in anaerobic bacteria and maintain the effectiveness of Clindamycin Injection, USP and other antibacterial drugs, Clindamycin Injection, USP should be used only if other agents are not suitable or not tolerated. This category indicates that the antimi-

Criteria

Table 2. Susceptibility Test Interpretive Criteria for Clindamycin

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Clindamycin Concentration (MIC)</th>
<th>Disk Diffusion (Zone Diameter mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp.</td>
<td>≤ 0.15</td>
<td>≤ 12</td>
</tr>
<tr>
<td>Staphylococcus pneumonia</td>
<td>≤ 0.15</td>
<td>≤ 12</td>
</tr>
<tr>
<td>Other Staphylococcus spp.</td>
<td>≤ 0.25</td>
<td>≤ 12</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>≤ 0.25</td>
<td>≤ 12</td>
</tr>
<tr>
<td>Actinomyces israelii</td>
<td>≤ 0.5</td>
<td>≤ 12</td>
</tr>
<tr>
<td>Peptostreptococcus anaerobius</td>
<td>≤ 1.0</td>
<td>≤ 12</td>
</tr>
<tr>
<td>Fusobacterium nucleatum</td>
<td>≤ 1.0</td>
<td>≤ 12</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS:

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.

WARNINGS:

REFERENCES


Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 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

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters, has not been associated with an increased frequency of congenital abnormalities.

Clindamycin should be used during the first trimester of pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (2.1 and 1.1 times the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (0.9 and 0.5 times the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

Clindamycin contains benzylic alcohol. Benzylic alcohol can cross the placenta (see WARNINGS). Nursing Mothers

Clindamycin has been reported to appear in breast milk in the range of 0.7 to 3.8 mcg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.

Pediatric Use

When clindamycin is administered to the pediatric population (birth to 16 years) appropriate monitoring of organ system functions is desirable.

Usage in Newborns and Infants

This product contains benzylic alcohol as a preservative. Benzylic alcohol has been associated with a fatal “Gasing Syndrome” in premature infants (see WARNINGS).

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.

Infections and Infestations

Clostridium difficile colitis.

Gastrointestinal

Antibiotic-associated colitis (see WARNINGS), pseudomembranous colitis, abdominal pain, nausea, and vomiting. The onset of pseudomembranous colitis symptoms may colitis symptoms occur during or after antibacterial treatment (see WARNINGS). An unpleasant or metallic taste has been reported after intravenous administration of the higher doses of clindamycin phosphate.

Hypersensitivity Reaction

Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate maculopapular skin rashes are the most frequently reported of all adverse reactions.

Severe skin reactions such as Toxic Epidermal Necrolysis, some with fatal outcome, have been reported (see WARNINGS). Cases of Acute Generalized Exanthematous Pustulosis (AGEP), erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. Anaphylactic shock, anaphylactic reaction and hypersensitivity have also been reported (see WARNINGS).

Skin and Mucous Membranes

Pruritus, vaginitis, angioedema 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.

Hematopoietic

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

Immune System

Drug reaction with eosinophilia and systemic symptoms (DRESS) cases have been reported.

Local Reactions

Injection site irritation, pain, induration and sterile abscesses have been reported after intramuscular injection and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

Musculoskeletal

Polyarthralgia cases have been reported.

Cardiovascular

Cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration (see DOSAGE AND ADMINISTRATION).

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 2,618 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 BOXED WARNING).

Clindamycin phosphate IV administration should be diluted (see Dilution for IV Use and IV Infusion Rates).

Adults

Parenteral 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 1,200 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: 1,200 to 2,700 mg/day in 2, 3 or 4 equal doses.

For more serious infections, 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 4,800 mg daily have been given intravenously to adults (see Dilution for IV Use and IV Infusion Rates).

Alternatively, drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion as follows:

To maintain serum clindamycin levels

<table>
<thead>
<tr>
<th>Rapid Infusion Rate</th>
<th>Maintenance infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 4 mcg/mL</td>
<td>10 mcg/min for 30 min</td>
</tr>
<tr>
<td></td>
<td>0.75 mcg/min</td>
</tr>
<tr>
<td>Above 5 mcg/mL</td>
<td>15 mcg/min for 30 min</td>
</tr>
<tr>
<td></td>
<td>1 mcg/min</td>
</tr>
<tr>
<td>Above 6 mcg/mL</td>
<td>20 mcg/min for 30 min</td>
</tr>
<tr>
<td></td>
<td>1.25 mcg/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 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 area.

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

Parenteral therapy may be changed to oral clindamycin flavored granules (clindamycin palmitate hydrochloride) or clindamycin hydrochloride caplet (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 for IV Use and IV Infusion Rates

Clindamycin Injection, USP must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 18 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>1,200 mg</td>
<td>100 mL</td>
<td>40 min</td>
</tr>
</tbody>
</table>
Administration of more than 1,200 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, penciillin or carbencillin.

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.fresenius-kabi.us](http://www.fresenius-kabi.us) or call Fresenius Kabi USA, LLC 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 33 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.

**DIRECTIONS FOR DISPENSING AND PROPER USE OF PHARMACY BULK PACKAGE**

**Pharmacy Bulk Package – Not for Direct Infusion**

The Pharmacy Bulk Package is for use in a Pharmacy Admixture Service only under a laminar flow hood. The exposed closure should be swabbed with a suitable aseptic solution. Entry into the vial should be made with a small diameter sterile transfer set or other small diameter sterile dispensing device, and contents dispensed in aliquots using aseptic technique. Multiple entries with a needle and syringe are not recommended. AFTER ENTRY USE ENTIRE CONTENTS OF VIAL PROMPTLY. ANY UNUSED PORTION MUST BE DISCARDED WITHIN 24 HOURS AFTER INITIAL ENTRY.

**HOW SUPPLIED:**

- Clindamycin Injection, USP, in the Pharmacy Bulk Package, supplied as clindamycin phosphate equivalent to clindamycin 150 mg/mL
- Clindamycin Injection, USP must be diluted and administered by manual or electromechanical injection pumps.

**Parenteral Drug Products**

- Solution: 9 grams per 60 mL in a 60 mL vial (150 mg per mL)

Packaged individually.

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

Do not refrigerate.

The container closure is not made with natural rubber latex.

**REFERENCES:**