PRODUCT MONOGRAPH

Pr CLINDAMYCIN INJECTION, USP

Clindamycin phosphate

150 mg/mL clindamycin (as clindamycin phosphate)

Sterile Solution

Antibiotic

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular Intravenous	Solution; clindamycin phosphate equivalent to 150 mg / mL of clindamycin base	9.45 mg/mL Benzyl alcohol, disodium edetate, sodium hydroxide hydrochloric acid (see **DOSAGE FORMS, COMPOSITION AND PACKAGING)**

INDICATIONS AND CLINICAL USE

CLINDAMYCIN INJECTION, USP (clindamycin phosphate) is indicated for the treatment of serious infections due to susceptible anaerobic bacteria, such as Bacteroides species, Peptostreptococcus, anaerobic streptococci, Clostridium species and microaerophilic streptococci.

CLINDAMYCIN INJECTION, USP is also indicated for the treatment of serious infections due to susceptible strains of gram positive aerobic bacteria (staphylococci, including penicillinase-producing staphylococci, streptococci and pneumococci) as well as in the treatment of *Chlamydia trachomatis,* when the patient is intolerant of, or the organism is resistant to other appropriate antibiotics.

Because of the risk of *Clostridium difficile*-associated disease (CDAD) as described in the WARNINGS section, before selecting clindamycin the physician should consider the nature of the infection and the suitability of alternative therapy.

CLINDAMYCIN INJECTION, USP is indicated for the treatment of the following serious infections when caused by susceptible strains of the designated organisms in the conditions listed below:

Lower respiratory infections including pneumonia, empyema, and lung abscess when caused by anaerobes, *Streptococcus pneumonia*e, other streptococci (except *Enterococcus faecalis*) and *Staphylococcus aureus*.

Skin and skin structure infections including cellulitis, abscesses, and wound infections when caused by *Streptococcus pyogenes*, *Staphylococcus aureus* and anaerobes.

Gynecological infections including endometritis, pelvic cellulitis, vaginal cuff infections, nongonococcal tubo-ovarian abscess, salpingitis, and pelvic inflammatory disease when caused by susceptible anaerobes or *Chlamydia trachomatis*. Clindamycin should be given in conjunction with an antibiotic of appropriate gram negative aerobic spectrum.

Intra-abdominal infections including peritonitis and abdominal abscess when caused by susceptible anaerobes. Clindamycin should be given in conjunction with an antibiotic of appropriate gram negative aerobic spectrum.

S**epticemia** caused by *Staphylococcus aureus*, streptococci (except *Enterococcus faecalis*) and susceptible anaerobes, where the bactericidal efficacy of clindamycin against the infecting organism has been determined *in vitro* at achievable serum levels.

Bone and joint infections including osteomyelitis and septic arthritis when caused by sensitive strains of *Staphylococcus aureus* and anaerobes.

***Pneumocystis* jiroveci pneumonia** in patients with AIDS. Clindamycin in combination with primaquine may be used in patients who are intolerant to, or fail to respond to conventional therapy.

Note: CLINDAMYCIN INJECTION, USP is not indicated in the treatment of meningitis since it penetrates poorly into cerebrospinal fluid, even in the presence of inflamed meninges.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

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

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 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.

Geriatrics (> 65 years of age):
Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients.

Pediatrics (birth up to 18 years of age):
It is not known if use of clindamycin in the pediatric population is associated with differences in safety or effectiveness compared with adult patients.

CONTRAINDICATIONS

CLINDAMYCIN INJECTION, USP (clindamycin phosphate) is contraindicated in patients with a known hypersensitivity to preparations containing clindamycin or lincomycin or to any ingredient in the formulation or component of the formulation.

WARNINGS AND PRECAUTIONS

General

In patients with G-6-PD deficiency, the combination of clindamycin with primaquine may cause hemolytic reactions. Reference should also be made to the primaquine product monograph for other possible risk groups for other hematologic reactions (see **ADVERSE REACTIONS**).

If patients should develop serious hematologic adverse effects, reducing the dosage regimen of primaquine and/or clindamycin should be considered (see DOSAGE and ADMINISTRATION).

CLINDAMYCIN INJECTION, USP (clindamycin phosphate) should be prescribed with caution in atopic individuals.

CLINDAMYCIN INJECTION, USP must be diluted for intravenous administration. It should not be injected undiluted as an intravenous bolus (see **DOSAGE and ADMINISTRATION**).

The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfections occur, appropriate measures should be taken as dictated by the clinical situation.

Care should be exercised when treating patients with multiple medications (see DRUG INTERACTIONS).

Gastrointestinal

CLINDAMYCIN INJECTION, USP should be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis, inflammatory bowel disease (including regional enteritis and ulcerative colitis), or a history of antibiotic-associated colitis (including pseudomembranous colitis).

NOTE: If diarrhea occurs during treatment, this antibiotic should be discontinued.

***Clostridium difficile*-associated disease (CDAD)**

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including clindamycin phosphate. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases. (see **ADVERSE REACTIONS**)

Hepatic/Biliary/Pancreatic
In patients with moderate to severe liver disease, prolongation of the half-life of clindamycin has been found. However, it was postulated from studies that when given every eight hours, accumulation of clindamycin should rarely occur. Therefore, dosage reduction in liver disease is not generally considered necessary. Periodic liver enzyme determinations should be made when treating patients with severe liver disease. (see PHARMACOLOGY)

Immune
Serious hypersensitivity reactions, including anaphylactoid reactions, severe skin reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS), and dermatological reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported in patients on clindamycin therapy. If a hypersensitivity reaction occurs clindamycin should be discontinued and appropriate therapy should be initiated (see CONTRAINDICATIONS, ADVERSE REACTIONS).

Renal
CLINDAMYCIN INJECTION, USP dose modification may not be necessary in patients with renal disease. The serum half-life of clindamycin is increased slightly in patients with markedly reduced renal function.

Susceptibility/Resistance
Prescribing CLINDAMYCIN INJECTION, USP in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Special Populations

Pregnant Women
There are no adequate and well-controlled studies in pregnant women. Safety for use in pregnancy has not been established.

Clindamycin should not be used in pregnancy unless clearly needed and unless the expected benefits to the mother outweigh any potential risks to the fetus. Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of

maternal blood concentrations. Clindamycin was widely distributed in fetal tissues with the highest concentration found in liver.

Clindamycin phosphate injectable formulation contains benzyl alcohol. The preservative benzyl alcohol can cross the placenta (see WARNINGS AND PRECAUTIONS).

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin ranging from 20 to 600 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to clindamycin except at doses that caused maternal toxicity. In one mouse strain, cleft palates were observed in treated fetuses; this response was not produced in other mouse strains or in other species, and therefore may be a strain specific effect.

Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

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

Pediatrics
Benzyl Alcohol Toxicity
CLINDAMYCIN INJECTION, USP injectable formulation contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome" and death in pediatric patients. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis and gasping respirations) has been reported in preterm and low birth weight newborns. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia and cardiovascular collapse.

Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic and renal capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources. When CLINDAMYCIN INJECTION, USP is administered to the pediatric population (birth to 16 years) appropriate monitoring of organ system functions is desirable.

Geriatrics (> 60 years of age)
Experience has demonstrated that antibiotic-associated colitis may occur more frequently and with increased severity among elderly (> 60 years) and debilitated patients. These patients should be carefully monitored for the development of diarrhea.

Monitoring and Laboratory Tests
Periodic liver and kidney function tests and blood counts should be performed during prolonged therapy when treating patients with severe liver disease.

Routine blood examinations should be done during therapy with primaquine to monitor potential hematologic toxicities.

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

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse drug reaction frequencies for the three clindamycin formulations (clindamycin capsules, clindamycin granules for oral solution and clindamycin injection) are based on the clinical data sources from the original drug submission and on the total number of patients enrolled in the clinical trials (N=1787).

Adverse drug reactions that were considered causally related to clindamycin and observed in ≥ 1% of patients are presented below in Table 1. They are listed according to MedDRA system organ class.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Patients treated with clindamycin within the Original Clinical Trials

Adverse Reaction **System Organ Class / Preferred Term**	**clindamycin** **Total N=1787[1]** **n (%)**
Gastrointestinal disorders	
Diarrhea	26 (1.45)
Investigations	
Liver function test abnormal	66 (3.7)
Skin and subcutaneous tissue disorders	
Rash maculopapular	21 (1.18)

[1]clindamycin hydrochloride capsules N=851; clindamycin granules for oral solution N=340; clindamycin phosphate injection N=596

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Less common adverse drug reactions that were considered causally related to clindamycin and observed in < 1% of patients are listed below.

Blood and lymphatic system disorders: Eosinophilia

Gastrointestinal disorders: Nausea, abdominal pain and vomiting.

General disorders and administration site conditions: Local irritation, pain, abscess formation have been seen with IM injection.

Nervous system disorders: Dysgeusia

Skin and subcutaneous tissue disorders: Urticaria, erythema multiforme and pruritus.

Post-Market Adverse Drug Reactions:

Additional adverse events which have been reported in temporal association with clindamycin formulations (clindamycin capsules, clindamycin granules for oral solution and clindamycin injection) since market introduction are listed below. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be established.

Blood and lymphatic system disorders: Agranulocytosis, leucopenia, neutropenia and thrombocytopenia. In clindamycin/primaquine combination studies, serious hematologic toxicities (grade III, grade IV neutropenia or anemia, platelet counts < 50 x 109/L, or methemoglobin levels of 15% or greater) have been observed.

Cardiac disorders: Cardio-respiratory arrest and hypotension have been seen with rapid intravenous administration (see **DOSAGE and ADMINISTRATION**).

Gastrointestinal disorders: Colitis and pseudomembranous colitis. Clostridium difficile-associated disease (CDAD) has been observed and may manifest as a range of symptoms varying from watery diarrhea to fatal colitis, the onset of which may occur during or after antibacterial treatment (see WARNINGS AND PRECAUTIONS). Esophagitis and esophageal ulcer have been reported with the oral formulations.

General disorders and administration site conditions: Injection site irritation, thrombophlebitis. These reactions can be minimized by deep IM injection and avoidance of indwelling intravenous catheters.

Hepatobiliary disorders: Jaundice

Immune system disorders: Generalized mild to moderate morbilliform-like skin rashes, anaphylactic shock, anaphylactoid reactions, anaphylactic reactions, hypersensitivity, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Infections and infestations: *Clostridium difficile* colitis
Musculoskeletal: Polyarthritis

Renal and urinary disorders: Renal dysfunction as evidenced by azotemia, oliguria and/or proteinuria

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), erythema multiforme, dermatitis exfoliative, dermatitis bullous, dermatitis vesiculobullous, rash morbilliform, vaginal infection, vaginitis, acute generalized exanthematous pustulosis (AGEP), angioedema.

Vascular disorders: Thrombophlebitis has been seen with rapid intravenous administration (see **DOSAGE and ADMINISTRATION**).

DRUG INTERACTIONS

Overview

Clindamycin is metabolized predominantly by CYP3A4, and to a lesser extent CYP3A5, to the major metabolite clindamycin sulfoxide and minor metabolite, N-desmethylclindamycin. Therefore inhibitors of CYP3A4 and CYP3A5 may reduce clindamycin clearance and inducers of these isoenzymes may increase clindamycin clearance.

In vitro studies indicate that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1, or CYP2D6 and only moderately inhibits CYP3A4. Therefore, clinically important interactions between clindamycin and coadministered drugs metabolized by these CYP enzymes are unlikely.

Clindamycin has been shown to have neuromuscular blocking properties and potential antagonism with erythromycin and aminoglycosides (see **Table 2**).

In a clindamycin/primaquine combination study, serious hematologic toxicity has been observed, but the contribution of clindamycin, if any, is unknown (see **ADVERSE REACTIONS**).

For other physicochemical interactions, please see to compatibility / incompatibility information in section **DOSAGE AND ADMINISTRATION**.

Drug-Drug Interactions

The drugs listed in the table below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 2 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Neuromuscular blocking agents Examples include: atracurium, doxacurium, pancuronium, vecuronium	CS	Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents.	Use with caution in patients receiving these agents concurrently.
aminoglycosides	T	Clindamycin is reported to antagonize bactericidal activity of aminoglycosides *in vitro*. *In vivo* antagonism has not been demonstrated.	
erythromycin	T	Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Clindamycin and erythromycin may compete for the same protein binding site in bacteria.	Due to possible clinical significance the two drugs should not be administered concurrently.
Inhibitors of CYP3A4, CYP3A5	T	Clearance of clindamycin may be reduced.	
Inducers of CYP3A4, CYP3A5	T	Clearance of clindamycin may be increased.	Monitor for loss of effectiveness.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Efficacy of clindamycin should be closely monitored in patients using concomitant St. John's Wort, a CYP3A4 inducer.

Drug-Laboratory Interactions

Interactions between clindamycin and laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

CLINDAMYCIN INJECTION, USP dose modification may not be necessary in patients with renal disease. Clindamycin injection dosage reduction in liver disease is not generally considered necessary.

Dosage adjustments are not necessary in the elderly with normal hepatic function and normal (age-adjusted) renal function.

Dosage and route of administration should be determined by the severity of the infection, the condition of the patient and the susceptibility of the causative microorganisms.

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

Recommended Dose and Dosage Adjustment

Adults

The usual daily adult dosage of CLINDAMYCIN INJECTION, USP for infections of the intra-abdominal area, female pelvis, and other complicated or serious infections is 2400-2700 mg given in 2, 3 or 4 equal doses. Less complicated infections may respond to lower doses such as 1200 - 1800 mg/day administered in 3 or 4 equal doses.

Doses of up to 4800 mg daily have been used without adverse effects. Single intramuscular doses of greater than 600 mg are not recommended.

Pelvic Inflammatory Disease:

Clindamycin 900 mg (IV) every 8 hours plus an antibiotic with appropriate gram negative aerobic spectrum administered IV. Treatment with intravenous drugs should continue for at least 48 hours after the patient demonstrates significant clinical improvement. Then continue with appropriate oral therapy to complete 10-14 days total therapy.

Pneumocystis jiroveci pneumonia in patients with AIDS:

Clindamycin 600-900 mg (IV) every 6 hours or 900 mg (IV) every 8 hours in combination with oral daily dose of 15-30 mg of primaquine. Alternatively, clindamycin hydrochloride 300-450 mg may be given orally every 6 hours in combination with 15-30 mg of primaquine for 21 days. If patients should develop serious hematologic adverse effects, reducing the dosage regimen of primaquine and/or clindamycin should be considered.

Children over one month of age (IM or IV Administration):

20-40 mg/kg/day in 3 or 4 equal doses. The higher doses would be used for more severe infections.

Neonates under one month of age (IM or IV Administration):

10-20 mg/kg/day in 3 or 4 equal doses. The lower dosage may be adequate for small prematures.

Table 3 – IM or IV Administration in Neonates			
Weight	**Age**	**Dose**	**Route**
< 2 kg	0-7 days	5 mg/kg q12h	IV
< 2 kg	8-30 days	5 mg/kg q8h	IV
≥ 2 kg	0-7 days	5 mg/kg q8h	IV
≥ 2 kg	8-30 days	5 mg/kg q6h	IV

NOTE: Injections of CLINDAMYCIN INJECTION, USP should be administered with caution to newborn infants less than 30 days of age. This product contains benzyl alcohol which has been associated with the fatal "gasping syndrome" in newborn infants. Preterm and low-birth weight infants may be more likely to develop toxicity (see **WARNINGS AND PRECAUTIONS**).

Administration
Injection site irritation can be minimized by deep IM injection and avoidance of indwelling intravenous catheters.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

IM Administration:
CLINDAMYCIN INJECTION, USP IM administration should be used undiluted.

IV Administration:
CLINDAMYCIN INJECTION, USP IV administration should be diluted.

Dilution for IV use and Infusion Rates:
CLINDAMYCIN INJECTION, USP must be diluted prior to intravenous administration (see **Compatibility with other products** for a listing of infusion solutions). The concentration in diluent for infusion should not exceed 18 mg/mL. Infusion rates should NOT EXCEED 30 MG PER MINUTE as indicated below:

Table 4 - Dilution and infusion rates		
Dose (mg)	**Diluent (mL)**	**Time (minutes)**
300	50	10
600	50	20
900	100	30
1200	100	45

Administration of more than 1200 mg in a single 1-hour infusion is not recommended.

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

Table 5 – Infusion rates per clindamycin levels		
To maintain serum clindamycin levels	**Rapid infusion rate**	**Maintenance infusion rate**
Above 4 mcg/mL	10 mg/min. for 30 min.	0.75 mg/min.
Above 5 mcg/mL	15 mg/min. for 30 min.	1.00 mg/min.
Above 6 mcg/mL	20 mg/min. for 30 min.	1.25 mg/min.

Compatibility with other products

CLINDAMYCIN INJECTION, USP was found to be compatible over a period of 24 hours when 4 mL (600 mg) of CLINDAMYCIN INJECTION, USP was diluted with 1000 mL of the following commonly used infusion solutions;

Sodium chloride injection
Dextrose 5% in water
Dextrose 5% in saline
Dextrose 5% in Ringer's Solution
Dextrose 5% in half-strength saline plus 40 mEq potassium chloride
Dextrose 2 1/2% in Lactated Ringer's Solution (Hartmann's Solution)

Clindamycin phosphate was not stable when added to Dextrose 5% in water plus vitamins. **Although CLINDAMYCIN INJECTION, USP is compatible with Dextrose 5% in water, it is not recommended that CLINDAMYCIN INJECTION, USP be mixed with any infusion solutions containing B vitamins.**

Clindamycin phosphate has been shown to be compatible with gentamycin sulfate, tobramycin sulfate and amikacin sulfate. However, a precipitate has been observed when Clindamycin phosphate and gentamicin are drawn undiluted into the same syringe before subsequent dilution. This precipitate appears to be a zinc-clindamycin complex which results from the zinc content of some gentamicin products. The particle size of the insoluble material is very small and disappears when the admixture is shaken. To avoid this problem, do not mix CLINDAMYCIN INJECTION, USP and gentamicin sulfate prior to dilution. Rather, dilute one drug or the other, agitate the solution and then add the second antibiotic.

Incompatibility with other products

When combined with clindamycin phosphate in an infusion solution, ampicillin, phenytoin sodium, barbiturates, aminophyllin, calcium gluconate, magnesium sulfate, ceftriaxone sodium, and ciprofloxacin are each physically incompatible with clindamycin phosphate.

Missed Dose:

If a dose is missed, it should be taken as soon as remembered unless it is almost time for the next dose. The dose should not be doubled to make up for a missed dose.

OVERDOSAGE

Reported cases of overdosage with clindamycin phosphate have occurred very infrequently. The majority of these reports have involved infants and young children ranging in age from one day to three years. In this age group, doses as high as 2.4 grams have been used intravenously in 36 hours without observation of adverse reactions. Cardio respiratory arrest and hypotension have been seen with rapid intravenous administration. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. No specific antidote is known. The serum elimination half-life of clindamycin is about 3 hours in adults and 2.5 hours in pediatric patients.

For management of suspected overdosage contact your regional Poison Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Following parenteral administration, biologically inactive clindamycin phosphate is rapidly hydrolyzed in plasma to active clindamycin. Clindamycin exerts its antibacterial effect by binding to the 50 S ribosomal subunit of susceptible bacteria, causing a reduction in the rate of synthesis of nucleic acid, and cessation of protein synthesis.

Clindamycin is primarily bacteriostatic, but may be bactericidal at high concentrations. The mechanism of action of clindamycin in combination with primaquine on *Pneumocystis jiroveci* is not known. (see DETAILED PHARMACOLOGY)

Pharmacodynamics

(see **MICROBIOLOGY**)

Pharmacokinetics

Absorption

An equilibrium state is reached by the third dose. After intramuscular injection, peak serum levels of clindamycin are reached within 3 hours in adults and 1 hour in pediatric patients. Peak serum levels of clindamycin are achieved immediately after the end of a short-term (10 to 45 minutes) intravenous infusion.

Distribution

Clindamycin binds primarily to alpha-1-acid glycoprotein. Protein binding is concentration dependent, ranging from 60% to 94% at therapeutic serum concentrations.

Clindamycin is distributed into body fluids and tissues including bone, synovial fluid, bile and pleural fluid. Significant levels of clindamycin are not reached in cerebrospinal fluid even in the presence of inflamed meninges. Clindamycin does not cross the blood-brain barrier even in the

presence of inflamed meninges. Clindamycin readily crosses the placenta and is distributed into breast milk.

Table 6 records tissue and body fluid levels of clindamycin base following administration of clindamycin phosphate in adult patients undergoing surgical procedures.

Table 6: Clindamycin concentrations in Tissues and Fluids

Specimen	Dosage of clindamycin phosphate	Tissue or Fluid Level
Bone	IM 300 mg every 8 hours	6.4 mcg/g
Bone	IM 600 mg every 8 hours	1.44 mcg/g
Bone	IV 600 mg every 8 hours	0.75 mcg/g
Bone Marrow	IM 600 mg every 8 hours	10.83 mcg/g
Bile	IV 300 mg every 6 hours	2.70 mcg/g
Synovial Fluid	IM 300 mg every 8 hours	4.87 mcg/mL
Synovial Fluid	IM 150 mg every 12 hours	15.6 mcg/mL
Pleural Fluid	IV 450 mg every 8 hours	3.65 mcg/mL

Table 7: Average Peak Serum Concentrations After Dosing with Clindamycin

Clindamycin Dosage Regimen	Clindamycin mcg/mL	Clindamycin mcg/mL
Healthy Adult Male (Post Equilibrium)		
300 mg IV in 10 min., q8h	7	15
600 mg IV in 20 min., q8h	10	23
900 mg IV in 30 min., q12h	11	29
1200 mg IV in 45 min., q12h	14	49
300 mg IM q8h	6	3
600 mg IM q12h *	9	3
Children (first dose)*		
5-7 mg/kg IV in 1 hour	10	
3-5 mg/kg IM	4	
5-7 mg/kg IM	8	

* Data in this group from patients being treated for infection

Metabolism

In vitro studies in human liver and intestinal microsomes indicate clindamycin is predominantly oxidized by CYP3A4, with minor contribution from CYP3A5, to form clindamycin sulfoxide and a minor metabolite, N-desmethylclindamycin.

Excretion

Approximately 10% of the microbiologically active form is excreted in the urine and about 4% in the feces. The remainder is excreted as biologically inactive metabolites.

Clindamycin phosphate disappears rapidly from the serum; the average elimination half-life is 6 minutes following IM or IV administration in adults. The serum elimination half-life of clindamycin is about 3 hours in adults and 2.5 hours in pediatric patients.

Special Populations and Conditions

Geriatrics

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. Therefore, dosage adjustments are not necessary in the elderly with normal hepatic function and normal (age-adjusted) renal function.

Hepatic Impairment

Six patients with impaired liver function had a mean serum elimination half-life of 4.5 hours (range 4.2 to 7.0 hours) (see DETAILED PHARMACOLOGY).

Renal Impairment

Four patients with impaired renal function had a mean serum elimination half-life of 3.0 hours (range 1.7 to 5.6 hours) (see DETAILED PHARMACOLOGY).

STORAGE AND STABILITY

Store CLINDAMYCIN INJECTION, USP at controlled room temperature (15 to 30°C). When diluted as recommended, CLINDAMYCIN INJECTION, USP is compatible for 24 hours.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of CLINDAMYCIN INJECTION, USP contains clindamycin phosphate equivalent to 150 mg of clindamycin base, benzyl alcohol 9.45 mg, disodium edetate 0.5 mg, nitrogen q.s. and water for injection q.s.

When necessary, the pH is adjusted with sodium hydroxide and/or hydrochloric acid to maintain a pH range of 5.5 to 7.0.

CLINDAMYCIN INJECTION, USP (clindamycin phosphate) is available in 2 mL, 4 mL and 6 mL vials containing 300 mg, 600 mg and 900 mg clindamycin (as clindamycin phosphate) respectively. All vial sizes are available in cartons of 10 vials.

2 mL:
A clear solution free from visible extraneous matter filled in 2 mL clear glass vials stoppered with 13 mm grey rubber stoppers and sealed with 13 mm orange flip-off seal.

4 mL:
A clear solution free from visible extraneous matter filled in 5 mL clear glass vials stoppered with 20 mm grey rubber stoppers and sealed with 20 mm brown flip-off seal.

6 mL:
A clear solution free from visible extraneous matter filled in 5 mL clear glass vials stoppered with 20 mm grey rubber stoppers and sealed with 20 mm white flip-off seal.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: clindamycin phosphate

Chemical Name:

1) L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, 2-(dihydrogen phosphate), (2S-trans)-;

2) Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pryrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate);

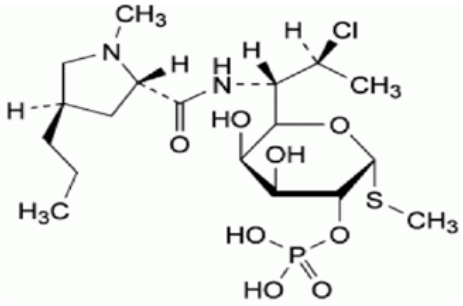
3) 7-(S)-Chloro-7-deoxylincomycin 2-phosphate.

4) Methyl 7-chloro-6,7,8 trideoxy-6-[[[(2S, 4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate)

Molecular Formula: $C_{18}H_{34}ClN_2O_8PS$

Molecular Weight: 505 g/mol

Structural Formula:



Description:

Clindamycin phosphate is a water soluble ester of clindamycin and phosphoric acid. It is a white to off white crystalline hygroscopic powder that is odourless or nearly odourless. It has a pH of 3.5 to 4.5 and melts with decomposition at about 175°C. The partition coefficient is 0.03.

CLINICAL TRIALS

The authorized indications were based on safety and efficacy clinical trials which were conducted with clindamycin injection.

DETAILED PHARMACOLOGY

Absorption and Excretion in Normal Human Volunteers:
Clindamycin phosphate is essentially inactive as the phosphate ester. Chemical or enzymatic hydrolysis of clindamycin phosphate is necessary to obtain the antibiotic activity of the clindamycin base. When tested with commercial human serum, clindamycin at a concentration of 1 mcg/mL of clindamycin free base is 92.8% protein bound.

Intramuscular: Serum levels and urinary excretion of clindamycin and clindamycin phosphate were measured after the single administration of 300 mg (2 mL) base equivalent of clindamycin phosphate and multiple dose administration (300 mg every 8 hours for 14 days). The results are shown in **Table 8.**

Table 8: Mean serum levels in mcg/mL of free clindamycin and clindamycin phosphate after 1st and 43rd IM dose of 300mg (2 mL) of clindamycin phosphate

	Hours after Injection								
	1st Injection							**43rd Injection**	
	0.5	**1**	**1.5**	**2**	**3**	**4**	**7.5**	**0**	**7.5**
Free clindamycin	2.05	3.16	3.66	3.88	3.89	3.56	1.94	2.85	2.67
Clindamycin phosphate	2.40	1.99	1.75	1.33	0.86	0.59	0.03	0.04	0.06

The apparent half-life of clindamycin phosphate is 3.5 to 4.5 hours. Bioavailability of clindamycin from its phosphate was estimated to be greater than 75%, based on urinary excretion of free clindamycin bioactivity (0 to 12 hours). During the multiple dose studies (300 mg every 8 hours for 14 days), there was no evidence of drug accumulation or enzyme induction.

Intravenous: Determination of serum levels of clindamycin and clindamycin phosphate after intravenous infusion of 300 to 1200 mg free base equivalents of clindamycin phosphate indicated that the concentrations of free clindamycin and intact phosphate were approximately equivalent during rapid infusion (see **Table 9**). The mean half-life of free clindamycin given by intravenous infusion is 2.28 hours for a 300 mg dose, 2.94 hours for a 600 mg dose, 3.27 hours for a 900 mg dose and 3.07 hours for a 1200 mg dose.

During maintenance infusion, free clindamycin (3.6 to 6.9 mcg/mL) was the predominant species in circulation. Over the total infusion period (0 to 8 hours) clindamycin and clindamycin phosphate were excreted in the urine in amounts up to 12.3% and 5.1% respectively of the

administered clindamycin phosphate dose. There was no indication that the capacity to excrete clindamycin in the urine had been taxed by these dosages.

Table 9: Mean serum levels in mcg/mL of free clindamycin and clindamycin phosphate after intravenous infusion of 300, 600, 900 and 1200 mg of clindamycin phosphate						
Dosage and Rate of Infusion		**Time after infusion began (in hours)**				
		A*	B*	1.5	4	12
300 mg in 10 minutes	Free clindamycin	5.40	4.36	3.49	1.66	0
	Clindamycin phosphate	14.66	2.35	0.43	0.13	-
600 mg in 20 minutes	Free clindamycin	8.42	6.70	5.88	3.04	0.62
	Clindamycin phosphate	26.98	2.24	0.58	0.28	0.02
900 mg in 30 minutes	Free clindamycin	10.37	8.02	7.10	4.18	1.08
	Clindamycin phosphate	31.20	3.18	1.29	0.25	0
1200 mg in 45 minutes	Free clindamycin	13.11	15.87	10.37	5.90	1.16
	Clindamycin phosphate	43.98	49.11	4.07	0.43	0

*	Time A	Time B
300 mg	0.17 hr	0.5 hr
600 mg	0.33 hr	0.75 hr
900 mg	0.5 hr	0.75 hr
1200 mg	0.5 hr	0.75 hr

Absorption and excretion in patients with impaired hepatic or renal function:

In a series of six patients with hepatic insufficiency and four patients with renal insufficiency, a single intravenous infusion of 300 mg of clindamycin phosphate was given over a period of 30 minutes. The results of these studies are summarized in **Tables 10, 11, 12** and **13**.

Table 10: Liver function tests in patients with impaired liver function					
Patient Number	**Total serum bilirubin**	**SGOT (K units)**	**SGPT (K units)**	**Alkaline Phosphatase**	**LDH**
1	7.0	150	-	150	180
2	6.6	155	74	110	-
3	8.0	35	-	50	100
4	1.6	135	-	235	-
5	>10	2200	-	130	340
6	>10	240	-	185	160

TABLE 11: Serum levels of free clindamycin in mcg/mL in patients with hepatic insufficiency, 300 mg clindamycin phosphate infused over 30 minutes.							
Patient Number	Time after start of infusion in hours						Elimination Half-Life (hrs)
	0.5	1.5	3	6	12	24	
1	7.19	3.61	3.36	1.96	0.74	-	4.9
2	11.60	6.32	5.25	4.04	2.23	1.30	7.0
3	8.68	7.16	5.15	3.68	1.25	0.88	4.4
4	17.75	8.60	6.08	2.77	0.83	0.0	4.8
5	8.42	4.93	3.84	2.49	0.75	0.45	4.2
6	9.51	4.63	3.38	2.66	1.31	0.0	5.8

TABLE 12: Renal function tests in patients with impaired renal function				
Patient Number	BUN	Serum creatinine	Urine albumin	Urine Sugar
1	87	3.4	2+	3+
2	73	3.2	2+	trace
3	78	6.4	4+	0
4	59	1.4	0	0

TABLE 13: Serum levels of free clindamycin in mcg/mL in patients with impaired renal function after 300 mg clindamycin phosphate infused over 30 minutes.							
Patient Number	Time after start of infusion in hours						Elimination Half-Life (hours)
	0.5	1.5	3	6	12	24	
1	12.07	7.35	5.26	2.30	1.08	0.0	3.0
2	12.00	4.15	3.36	1.90	0.66	0.42	3.6
3	15.25	10.63	7.52	5.80	-	1.41	5.6
4	11.26	7.29	3.39	1.60	0.0	0.0	1.7

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.

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 in Table 14 by application of elimination half- lives (see **Excretion**).

Table 14. Average Peak and Trough Serum Concentrations of Active Clindamycin After Dosing with Clindamycin Phosphate

Dosage Regimen	Peak mcg/mL	Trough mcg/mL
Healthy Adult Males (Post equilibrium)		
600 mg IV in 30 min q6h	10.9	2.0
600 mg IV in 30 min q8h	10.8	1.1
900 mg IV in 30 min q8h	14.1	1.7
600 mg IM q12h*	9	
Pediatric Patients (first dose)*		
5–7 mg/kg IV in 1 hour	10	
5–7 mg/kg IM	8	
3–5 mg/kg IM	4	

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

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations 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.

Excretion

The mean elimination half-time for normal healthy men given 300 mg of clindamycin phosphate in a 10 minute infusion was 2.5 hours. The six patients with impaired liver function had a mean elimination half-time of 4.5 hours and those with impaired renal function a mean elimination half-time of 3.0 hours.

MICROBIOLOGY

Clindamycin phosphate is inactive *in vitro,* but is rapidly converted *in vivo* to the antibacterially-active clindamycin.

In order to assess the significance of *in vitro* antibiotic activity against bacterial species, it is necessary to compare the organism's minimum inhibitory concentration (MIC) to the defined susceptibility interpretive breakpoints for the antibiotic. **Table 15** identifies the currently-accepted NCCLS (1990) MIC interpretative breakpoints for clindamycin.

Table 15. Susceptibility Interpretive Criteria for Clindamycin

Pathogen	Susceptibility Interpretive Criteria					
	Minimal Inhibitory Concentrations (MIC in mcg/mL)			Disk Diffusion (Zone Diameters in mm)		
Staphylococcus spp.	**S** ≤ 0.5	**I** 1–2	**R** ≥4	**S** ≥21	**I** 15–20	**R** ≤14

Table 15. Susceptibility Interpretive Criteria for Clindamycin						
Pathogen	**Susceptibility Interpretive Criteria**					
	Minimal Inhibitory Concentrations (MIC in mcg/mL)			**Disk Diffusion (Zone Diameters in mm)**		
Streptococcus pneumoniae and other *Streptococcus* spp.	≤0.25	0.5	≥1	≥19	16–18	≤15
Anaerobic Bacteria	≤2	4	≥8	NA	NA	NA

NA = not applicable

The reported clindamycin MIC_{90} value (i.e., the concentration of clindamycin that inhibits 90% of test isolates) was utilized as the most descriptive measure of clindamycin activity. Where the data from more than one study are summarized, the weighted average MIC_{90} value was calculated to account for differences in the number of strains in each study.

The *in vitro* susceptibility of clinical isolates to clindamycin is presented in **Table 16** (gram-positive aerobic bacteria), **Table 17** (gram-negative aerobic bacteria), **Table 18** (gram-positive anaerobic bacteria), **Table 19** (gram-negative anaerobic bacteria) and **Table 20** (*Chlamydia* spp and *Mycoplasma* spp).

Table 16: *In vitro* activity of clindamycin against gram-positive aerobic bacteria[a]			
Organism	**N[b]**	**MIC_{90} Range[c]**	**MIC_{90} [d]**
Bacillus cereus	46	1	1
Corynebacterium diphtheriae	192	0.1	0.1
Listeria monocytogenes	218	1-8	2.22
Staphylococcus aureus (methicillin-susceptible)	286	0.12-2	0.50
Staphylococcus saprophyticus	57	0.12-0.25	0.16
Streptococcus agalactia	59	≤ 0.06-0.50	0.15
Streptococcus bovis	22	0.04	0.04
Streptococcus pneumonia (penicillin-susceptible)	660	0.03-0.25	0.23
Streptococcus pyogenes	141	0.13-0.25	0.08
Streptococcus spp, *Group B*	38	≤ 0.12-0.25	0.15
Streptococcus spp, *Group C*	30	≤ 0.12-0.50	0.22
Streptococcus spp, *Group G*	34	0.06-0.50	0.31
Streptococcus spp, viridans Group (penicillin-susceptible)	67	≤ 0.06-1.6	0.53

[a] clinical efficacy has not been established for some of these species
[b] N, total number of isolates
[c] Range of reported MIC90 values
[d] MIC_{90} for single study or weighted average MIC_{90} for two or more studies

Table 17: *In vitro* activity of clindamycin against gram-negative aerobic bacteria[a]			
Organism	**N[b]**	**MIC_{90} Range[c]**	**MIC_{90} [d]**
Campylobacter jejuni	449	0.39-8	1.7
Campylobacter fetus	41	1-1.6	1.2
Campylobacter coli	31	0.50	0.50
Gardnerella vaginalis	156	≤ 0.06-0.39	0.3
Helicobacter pylori	47	2-3.1	2.6
Neisseria gonorrhoeae (β-lactamase-negative)	77	4	4

Table 17: *In vitro* activity of clindamycin against gram-negative aerobic bacteria[a]			
Organism	**N[b]**	**MIC_{90} Range[c]**	**MIC_{90} [d]**
Neisseria gonorrhoeae (β-lactamase-positive)	54	2	2

[a] clinical efficacy has not been established for some of these species
[b] N, total number of isolates
[c] Range of reported MIC90 values
[d] MIC_{90} for single study or weighted average MIC_{90} for two or more studies

Table 18: *In vitro* activity of clindamycin against gram-positive anaerobic bacteria[a]			
Organism	**N[b]**	**MIC_{90} Range[c]**	**MIC_{90} [d]**
Actinomyces israelii	46	0.12	0.12
Actinomyces spp	38	0.50-1	0.8
Clostridium botulinum	224	4	4
Clostridium difficile	191	4->256	57.7
Clostridium novyi	18	2	2
Clostridium perfringens	386	0.25-8	3.4
Clostridium ramosum	98	4-12.5	8.3
Eubacterium spp	45	0.4-2	1.1
Lactobacillus spp	88	0.50-1	0.8
Peptostreptococcus anaerobes	283	0.25-0.50	0.4
Peptostreptococcus asaccharolyticus	268	0.25-2	1.5
Peptostreptococcus magnus	90	2	2
Peptostreptococcus prevotii	87	0.12-4	2.9
Peptostreptococcus tetradius	28	0.5	0.5
Anaerobic gram-positive cocci	247	0.5-1	0.9
Propionibacterium acnes	267	0.10-0.25	0.2
Propionibacterium spp	71	0.12-0.20	0.16

[a] clinical efficacy has not been established for some of these species
[b] N, total number of isolates
[c] Range of reported MIC_{90} values
[d] MIC_{90} for single study or weighted average MIC_{90} for two or more studies

Table 19: *In vitro* activity of clindamycin against gram-negative anaerobic bacteria[a]			
Organism	**N[b]**	**MIC_{90} Range[c]**	**MIC_{90} [d]**
Bacteroides fragilis group	4,284	0.5-8	2.45
Bacteroides fragilis	2,002	≤ 0.20-4	2.22
Bacteroides melaninogenicus	224	≤ 0.03-0.50	0.07
Bacteroides spp	141	≤ 0.06-0.50	0.31
Bacteroides bivius	155	≤ 0.03-≤ 0.05	≤ 0.11
Bacteroides disiens	33	≤ 0.03-≤ 0.06	≤ 0.05
Fusobacterium spp	330	≤ 0.10-2	0.85
Mobiluncus mulieris	10	0.06	0.06
Mobiluncus curtisii	12	0.12	0.12
Veillonella spp	38	0.06-0.25	0.20

[a] clinical efficacy has not been established for some of these species
[b] N, total number of isolates
[c] Range of reported MIC90 values
[d] MIC_{90} for single study or weighted average MIC_{90} for two or more studies

Clindamycin has demonstrated in vitro activity against Chlamydia trachomatis and Mycoplasma spp (see Table 20). For Chlamydia trachomatis, the MIC_{90} for clindamycin is reached at 2.3 µg/mL; in vitro synergism with gentamicin has also been demonstrated.

Table 20: *In vitro* activity of clindamycin against *Chlamydia* spp and *Mycoplasma* spp [a]

Organism	N[b]	MIC_{90} Range[c]	MIC_{90} [d]
Chlamydia trachomatis	84	0.5-5.9	2.3
Mycoplasma hominis	106	0.25-0.8	0.58
Mycoplasma pneumoniae	9	4	4

[a] clinical efficacy has not been established for some of these species
[b] N, total number of isolates
[c] Range of reported MIC_{90} values
[d] MIC_{90} for single study or weighted average MIC_{90} for two or more studies

The *in vitro* activity of clindamycin in combination with primaquine has not been determined.

Development of resistance to clindamycin by staphylococci is slow and stepwise rather than rapid and streptomycin-like. Clindamycin, like lincomycin, participates in the dissociated cross-resistance phenomenon with erythromycin. Clindamycin is not cross-resistant with penicillin, ampicillin, tetracycline or streptomycin. It is, however, cross-resistant with lincomycin.

Resistance to clindamycin may occur by one of several mechanisms. Resistance does not appear to be caused by reduced drug uptake but rather is generally due to alterations in the bacterial target site (50S ribosomal subunit). Resistance can result from either changes in a ribosomal protein at the receptor site or a change in the 23S ribosomal RNA by methylation of adenine. Rare isolates of staphylococci and some veterinary isolates of streptococci may enzymatically inactivate clindamycin by adenylation. Plasmid-mediated transferable resistance to clindamycin (and erythromycin) in *B.fragilis* was reported in 1979.

Despite the existence of multiple resistance mechanisms, the reported incidence of clindamycin resistance in the *B.fragilis* group has remained relatively low (averaging 5.3% from 1970-1987 in over 7,600 isolates). Susceptibility of isolates to clindamycin should be assessed by individual MIC determinations.

TOXICOLOGY

Acute Toxicity

The results of LD_{50} studies are shown in **Table 21**:

TABLE 21: LD50 Results

Species	Route	LD50 (mg/kg)
Adult Mouse	IP	1145
Adult Mouse	IV	855
Adult Rat	SC	>2000
Adult Rat	PO	1832
Newborn Rat	SC	179

Tables 22 and **23** summarize toxicity and teratology studies. **Table 24** summarizes human studies.

Teratogenic and Reproductive Studies in the Rat and Rabbit

Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin, except at doses that caused maternal toxicity.

In oral embryo fetal development studies in rats and subcutaneous embryo fetal development studies in rats and rabbits, no developmental toxicity was observed except at doses that produced maternal toxicity.

Mutagenicity

Clindamycin phosphate did not show evidence of mutagenicity when tested in the Ames Assay (Salmonella/Microsome Test) or the Micronucleus Test.

Carcinogenesis

Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential.

Table 22 - TOXICITY STUDIES

Type of Study	Species	Route	Dose mg/kg/d	Duration	Conclusions
Tolerance	Rabbit N=3	im	100,200, 300 mg	single dose	Slight to moderate local irritation
Tolerance	Rat N=10	sc	120	6 days	Local evidence of multiple epidermal breakdown with scab formation over the injection site was present in most rats. No systemic evidence of drug effect was detected at necropsy. Organ weights were not significantly different from control animals and likewise no significant deviations of hematologic data were noted among treated animals.
Tolerance	Dog N=3	im	60	6 days	These doses were well tolerated by the dogs. Serum transaminase values were elevated terminally with SGOT values increasing in advance of SGPT values, suggesting that the source of these changes was the injected muscles. No other evidence of treatment-related changes was noted in terminal hemograms, blood chemistry values and urinalyses. Gross pathological changes were confined to the injection sites where there were signs of slight hemorrhage and edema.
Subacute Toxicity	Rat N=10	sc	30,60,90	1 month	No drug-related systemic effects were observed. Local inflammatory changes were seen at all three dose levels with focal necrosis of the subcutaneous tissues and overlying epidermis seen in the 60 and 90 mg/kg groups.
Subacute Toxicity	Dog N=9	im	30,60,90	1 month	Under the conditions of this study, clindamycin phosphate was found to be mildly to moderately irritating. Elevations of SGOT and SGPT were noted in these dogs and were thought to be due to muscle damage caused by the injections. Other blood evaluations and liver function tests were in the normal range. A slight dose-related increase in liver weight was indicated on the basis of per cent of body weight, but no morphologic evidence of drug effect on the liver was obtained.
Subacute Toxicity	Dog N=8	iv	60,120	1 month	No drug related effects were observed in any of the animals during or after the intravenous administrations. In particular, there was no evidence of drug-induced hemolysis or drug-related changes in the cephalic veins on both gross and microscopic examination.

Table 23 - TERATOLOGY STUDIES				
Species	**Route**	**Dose mg/kg/day**	**Duration**	**Conclusions**
Rat	sc	0, 100, 180	gestation days 6-15	not teratogenic
Mouse	sc 2 strains	100, 180	gestation days 6-15	A low incidence of cleft palate occurred in one strain in the initial experiment and as a result, the study was repeated twice with no abnormalities noted. The study in the second strain of mice was completely within normal limits.
Rat	po	100, 300		No biologically significant effect on the reproductive parameters studied was noted. Pups from treated females were slightly lighter at birth and weaning but post-natal survival was not affected by this slight weight reduction. None of the pups which were dead at birth, died before weaning, or were sacrificed at weaning, exhibited significant morphologic abnormalities.

Table 24 - HUMAN TOLERANCE STUDIES				
N	**Route**	**Dose**	**Duration**	**Conclusions**
8	im	300 mg clindamycin phosphate	Single dose	Subjectively, one patient had mild pain, four had moderate pain and two had marked pain which did not occur immediately, but reached its maximum at 10 to 30 minutes after injection and subsided to a mild ache 30 to 60 minutes later. Clinical laboratory findings were all normal.
8	im	600 mg clindamycin phosphate	Single dose	Only three patients had short-lived moderate pain 30 minutes after injection.
24	im	Group 1 (8 patients): 300 mg clindamycin phosphate	every 8 hr (total 43 injections)	One volunteer in each of the clindamycin phosphate and Lincocin group was removed from the study after 41 injections due to local intolerance. One volunteer from sodium chloride group left on day 5 (after 15 injections) complaining that the injections were too painful. Three Lincocin volunteers were dropped from the study on day 8 (after 24 injections); one due to local discomfort and a suspected viral illness; one due to a rash and one because of headache and tinnitus. In general, in these small groups, clindamycin phosphate was as well tolerated as Lincocin. There was no necrosis in any case. Pain, tenderness, swelling and induration were typically mild. Two clindamycin phosphate-treated volunteers developed mild cases of loose stools, lasting two to ten days during treatment. Audiometric examinations showed no change from pre-treatment examinations. Clinical laboratory findings did not indicate any drug-induced toxicity. A marked rise in creatinine phosphokinase was seen in both the clindamycin phosphate and Lincocin groups. SGOT also rose above normal in the clindamycin group, but not in the Lincocin group. SGPT findings remained within normal range in all groups. These changes are
		Group 2 (8 patients): 2 mL of sodium chloride injection USP		
		Group 3 (8 patients): 600 mg Lincocin sterile solution		

<table>
<tr><th colspan="10">Table 24 - HUMAN TOLERANCE STUDIES</th></tr>
<tr><th>N</th><th>Route</th><th colspan="7">Dose</th><th>Duration</th><th>Conclusions</th></tr>
<tr><td></td><td></td><td colspan="7"></td><td></td><td>consistent with changes due to muscle irritation and not attributed to liver damage.</td></tr>
<tr><td rowspan="6">20</td><td rowspan="6">iv</td><td colspan="7">Dosing Schedule</td><td rowspan="6">five days</td><td rowspan="6">Tolerance observations included blood pressure, pulse, respiratory rate and lead II electrocardiographic monitoring prior to, every 5 minutes during and at the end of each infusion. A 12 lead electrocardiographic tracing was done prior to treatment and after the 12th infusion. Audiograms were performed prior to treatment, within 48 hours after and 90 days after the 12th infusion. Subjects were watched closely for signs of local intolerance during each infusion period. Prior to the 1st, 5th, 9th and 4 hours after the 12th infusion, blood and urine samples were obtained for the following clinical laboratory determinations: complete blood count (CBC); complete urinalysis; serum glutamic oxalacetic transaminase (SGOT); serum alkaline phosphatase; serum creatinine; total, direct and indirect bilirubin; urine bilirubin; and serum haptoglobin. None of the tolerance data indicated any clinically significant side effects from the intravenous infusion of clindamycin phosphate.</td></tr>
<tr><td>Subject Nos.</td><td>Treatment Group</td><td>Dose (mg)</td><td>Infusion Regimen</td><td>Infusion Rate</td><td>Total Daily Dose (mg)</td></tr>
<tr><td>1-6</td><td>A</td><td>300</td><td>4 doses bid
4 doses tid
4 doses qid</td><td>30 mg/minute for 10 minutes</td><td>600
900
1200</td></tr>
<tr><td>7-12</td><td>B</td><td>600*</td><td>4 doses bid
4 doses tid
4 doses qid</td><td>30 mg/minute for 20 minutes</td><td>1200
1800
2400</td></tr>
<tr><td>13-16</td><td>C</td><td>900</td><td>4 doses bid
4 doses tid
4 doses qid</td><td>30 mg/minute for 30 minutes</td><td>1800
2700
3600</td></tr>
<tr><td>17-20</td><td>D</td><td>1200</td><td>4 doses bid
4 doses tid
4 doses qid</td><td>26.7 mg/minute for 45 minutes</td><td>2400
3600
4800</td></tr>
</table>

* Subject 7 and 8 received 1200 mg in 20 minutes on infusion #1

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PART III: PATIENT MEDICATION INFORMATION

PrCLINDAMYCIN INJECTION, USP
Sterile Solution

Read this carefully before you start taking CLINDAMYCIN INJECTION, USP and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about CLINDAMYCIN INJECTION, USP.

Antibacterial drugs like CLINDAMYCIN INJECTION, USP treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, CLINDAMYCIN INJECTION, USP should be taken exactly as directed. Misuse or overuse of CLINDAMYCIN INJECTION, USP could lead to the growth of bacteria that will not be killed by CLINDAMYCIN INJECTION, USP (resistance). This means that CLINDAMYCIN INJECTION, USP may not work for you in the future.

What CLINDAMYCIN INJECTION, USP is used for:
CLINDAMYCIN INJECTION, USP is used for the treatment of serious bacterial infections.

How does CLINDAMYCIN INJECTION, USP work?
CLINDAMYCIN INJECTION, USP reduces the production of key protein in germs. This prevents growth in germs and reduces the infection.

What are the ingredients in CLINDAMYCIN INJECTION, USP:
Medicinal ingredients: Clindamycin phosphate.
Non-medicinal ingredients: Each mL of undiluted CLINDAMYCIN INJECTION, USP contains benzyl alcohol 9.45 mg, disodium edetate 0.5 mg, sodium hydroxide (for pH adjustment), dilute hydrochloric acid (for pH adjustment), nitrogen and sterilised water for injection

CLINDAMYCIN INJECTION, USP comes in the following dosage forms:
CLINDAMYCIN INJECTION, USP is a clear, colourless solution. It is supplied in glass vials containing 2 ml, 4 ml or 6 ml of undiluted sterile solution containing 150 mg/mL clindamycin (as clindamycin phosphate).

Do not use CLINDAMYCIN INJECTION, USP if:
- You are allergic (hypersensitive) to
  - Clindamycin
  - Lincomycin
  - Other ingredients in the product (see list of non-medicinal ingredients).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CLINDAMYCIN INJECTION, USP. Talk about any health conditions or problems you may have, including if you:
- have had intestinal disorders such as:
  - colitis (inflammation of the colon)
  - inflammatory bowel disease.
- have diarrhea or get diarrhea when you take antibiotics.
- suffer from problems with your stomach or intestines (e.g. bowel disease, colitis).
- suffer from problems with your kidneys or liver
- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed.
- you are taking primaquine for an enzyme deficiency called glucose-6-phosphate dehydrogense (G-6-PD). You need to have routine blood tests, to monitor for potential blood cell changes.

Other warnings you should know about:
CLINDAMYCIN INJECTION, USP contains benzyl alcohol which may be harmful to newborns and children up to 3 years old.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. The following may interact with CLINDAMYCIN INJECTION, USP:
- Erythromycin (an antibiotic)
- Muscle relaxants used during operations.
- Primaquine (antimalarial)
- Aminoglycosides (a class of antibiotics)
- St. John's Wort (*Hypericum perforatum*)

How to take CLINDAMYCIN INJECTION, USP:
The health care professional will administer CLINDAMYCIN INJECTION, USP and will:
- Decide whether the medicine should be:
  - injected into a vein or
  - injected into a muscle
- Ensure that:
  - the medicine will be diluted before it is administered into a vein.
  - medicine will not be diluted if administered into a muscle
  - the medicine will be given for the full treatment period
  - the medicine will be inspected to determine there is:
    - no discolouration
    - no leaks
    - no solid particles floating in solution
    - no haziness in the solution

Usual dose:
Your doctor will determine the dose and for how long you should receive it.

Long term use of **CLINDAMYCIN INJECTION, USP**:

- If you have to use for a long time, your doctor may arrange regular liver, kidney and blood tests.
- Do not miss these check-ups with your doctor.
- Long term use can also make you more likely to get other infections that do not respond to clindamycin treatment.

Overdose:

If you think you have taken too much CLINDAMYCIN INJECTION, USP, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you missed a dose of this medication, take it as soon as you remember. This will help to keep a constant amount of medication in your blood. But, if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using CLINDAMYCIN INJECTION, USP?

These are not all the possible side effects you may feel when taking CLINDAMYCIN INJECTION, USP. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

CLINDAMYCIN INJECTION, USP can cause side effects such as:
- skin reddening, rash, itching, hives
- throat ulcers, sore throat
- feeling sick, being sick
- stomach pain and diarrhea
- injection site irritation
- thrombophlebitis (inflammation of the vein due to blood clot)
- low red blood cells (anemia) with symptoms such as bruising, bleeding
- low white blood cells (neutropenia) which can lead to infections
- vaginal infection or vaginitis (inflamed vagina)

Contact your doctor immediately if the following happens:
- You have a severe allergic reaction with symptoms such as:
  - sudden wheeziness
  - difficulty in breathing
  - swelling of eyelids, face or lips
  - rash or itching (especially affecting the whole body)
- Blistering and peeling of large areas of skin
  - Fever
  - Cough
  - Feeling unwell
  - Swelling of the gums, tongue or lips
- You have liver problems with symptoms such as:
  - yellowing of the skin and whites of the eyes (jaundice)
- You have Clostridium difficile colitis (bowel inflammation) with symptoms such as:
  - severe, persistent watery or bloody diarrhea (watery or bloody) with or without
    - abdominal pain
    - nausea
    - fever
    - vomiting

This may happen months after the last dose of medication. If this occurs, stop taking and contact your doctor right away.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON **Liver problems** with symptoms such a yellowing skin or eyes, abdominal pain, nausea, vomiting		√	√
COMMON Diarrhea Rash		√ √	
RARE Skin reactions : itching	√		
NOT KNOWN **Clostridium difficile associated disease** (bowel inflammation), with symptoms such as persistent or severe diarrhea, abdominal pain, nausea and vomiting			√
Injection site reactions with symptoms as pain, redness and skin irritation	√		
Serious allergic (hypersensitivity) reaction with symptoms such as swelling of eyes, mouth, throat, difficulty breathing, blistering or peeling skin, rash, itching			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your health care professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting

Form and sending it by:

- Fax to 1-866-678-6789 (toll-free), or
- Mail to: Canada Vigilance Program
  Health Canada, Postal Locator 0701E
  Ottawa, ON
  K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep out of the reach and sight of children.
- This medicine should be stored at controlled room temperature between 15 and 30°C.
- This medicine should not be refrigerated or frozen

If you want more information about CLINDAMYCIN INJECTION, USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; or by calling 1-800-575-1379
- This document can be found at: www.mylan.ca.

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