PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] CLINDAMYCIN INJECTION USP

Clindamycin Injection

Sterile Solution, 150 mg / mL clindamycin (as clindamycin phosphate), Intravenous, Intramuscular

USP

Antibiotic

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	06/2022
7 WARNINGS AND PRECAUTIONS, Renal	06/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Clindamycin Injection USP (clindamycin injection) 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 7 WARNINGS AND PRECAUTIONS section, before selecting clindamycin the healthcare professional 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 pneumoniae*, 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, non-gonococcal 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.

- **Septicemia** 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.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of clindamycin injection in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use. It is not known if use of clindamycin in the pediatric population is associated with differences in safety or effectiveness compared with adult patients.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

Clindamycin Injection USP 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. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Clindamycin Injection USP dose modification may not be necessary in patients with renal disease.

Clindamycin Injection USP 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.

4.2 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 Injection USP 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 Injection USP 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 Injection USP should be considered.

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

Clindamycin should be dosed based on total body weight regardless of obesity.

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 1. 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: Clindamycin Injection USP multidose formulation 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 7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics).

4.3 Reconstitution

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 2. 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 3. Infusion rates per clindamycin levels

To maintain serum clindamycin levels	Rapid infusion rate	Maintenance infusion rate

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 was found to be compatible over a period of 24 hours when 4 mL (600 mg) of clindamycin injection was diluted with 1000 mL of the following commonly used infusion solutions:

Sodium chloride 0.9%
Dextrose 5% in water

Clindamycin injection 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 injection has been shown to be compatible with gentamicin sulfate, tobramycin sulfate and amikacin sulfate. However, a precipitate has been observed when clindamycin injection 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 injection in an infusion solution, ampicillin, phenytoin sodium, barbiturates, aminophyllin, calcium gluconate, magnesium sulfate, ceftriaxone sodium, and ciprofloxacin are each physically incompatible with clindamycin injection.

4.4 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 should be used undiluted.

IV Administration

Clindamycin Injection USP should be diluted.

4.5 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.

5 OVERDOSAGE

Reported cases of overdosage with clindamycin injection 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. Cardiorespiratory 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 a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular, Intravenous	Solution; clindamycin phosphate equivalent to 150 mg / mL of clindamycin base	Preservative-free Formulation: disodium edetate, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection. Multidose Formulation (benzyl alcohol-preserved): benzyl alcohol as preservative, disodium edetate, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.

Clindamycin Injection USP is available as a preservative-free and a benzyl alcohol-preserved Multidose Formulation as follows:

Preservative-free Formulation:
2 mL, 4 mL and 6 mL single-use glass vials, in boxes of 10. Discard unused portion.

Pharmacy Bulk Vials of 60 mL. **The availability of the Pharmacy Bulk Vial is limited to hospitals with a pharmacy based IV admixture program. The Pharmacy Bulk Vial is intended for single**

puncture, multiple dispensing for intravenous infusion only. Dispensing from the Pharmacy Bulk Vial should be completed within 8 hours of initial puncture.

Multidose Formulation (benzyl alcohol-preserved):
2 mL, 4 mL and 6 mL multiple-dose glass vials, in boxes of 10. Discard within 28 days after initial puncture.

Pharmacy Bulk Vials of 60 mL. **The availability of the Pharmacy Bulk Vial is limited to hospitals with a pharmacy based IV admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing for intravenous infusion only.**

7 WARNINGS AND PRECAUTIONS

General
Clindamycin Injection USP must be diluted for intravenous administration. It should not be injected undiluted as an intravenous bolus (see 4 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 9 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 injection. 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 8 ADVERSE REACTIONS).

Hematologic
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 8 ADVERSE REACTIONS).

If patients should develop serious hematologic adverse effects, reducing the dosage regimen of primaquine and/or Clindamycin Injection USP should be considered (see 4 DOSAGE AND ADMINISTRATION).

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 10 CLINICAL PHARMACOLOGY).

Immune
Clindamycin Injection USP should be prescribed with caution in atopic individuals

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 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

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 injection.

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.

Clindamycin is potentially nephrotoxic. Acute kidney injury including acute renal failure has been reported. Therefore, monitoring of renal function should be considered during therapy of patients with pre-existing renal dysfunction or taking concomitant nephrotoxic drugs and monitoring of renal function should be performed if therapy is prolonged.

Sensitivity/Resistance
Development of drug-resistant bacteria
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.

7.1 Special Populations

7.1.1 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 Injection USP multidose formulation contains benzyl alcohol. The preservative benzyl alcohol can cross the placenta (see 7 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.

7.1.2 Breast-feeding

Clindamycin has been reported to appear in human breast milk in the ranges from <0.5 to 3.8 mcg/mL.

Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhea or blood in the stool, or rash. Because of the potential for serious adverse reactions in nursing infants, if clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. If Clindamycin Injection USP is used by a nursing mother, monitor the infant for possible adverse effects on the gastrointestinal flora, such as diarrhea, candidiasis (thrush, diaper rash) or blood in the stool indicating possible antibiotic-associated colitis.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Clindamycin Injection USP and any potential adverse effects on the breastfed child from Clindamycin Injection USP or from the underlying maternal condition.

7.1.3 Pediatrics

Benzyl Alcohol Toxicity
Clindamycin Injection USP multidose 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.

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 5. They are listed according to MedDRA system organ class.

Table 5. 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 injection N=596

8.3 Less Common Clinical Trial Adverse Reactions

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.

8.5 Post-Market Adverse 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 10^9/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 4 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 7 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.

Acute kidney injury including acute renal failure has been reported. (see 7 WARNINGS AND PRECAUTIONS)

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 4 DOSAGE AND ADMINISTRATION).

9 DRUG INTERACTIONS

9.2 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 the presence of strong CYP3A4 inducers such as rifampin, monitor for loss of effectiveness.

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 6).

In a clindamycin/primaquine combination study, serious hematologic toxicity has been observed, but the contribution of clindamycin, if any, is unknown (see 8 ADVERSE REACTIONS).

For other physicochemical interactions, please see to compatibility / incompatibility information in section 4 DOSAGE AND ADMINISTRATION.

9.4 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 6. Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Neuromuscular blocking agents Examples include:	CS	Clindamycin has been shown to have neuromuscular blocking properties	Use with caution in patients receiving these agents concurrently.

Proper name	Ref	Effect	Clinical comment
atracurium, doxacurium, pancuronium, vecuronium		that may enhance the action of other neuromuscular blocking agents.	
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.
Strong inducers of CYP3A4 such as rifampin	CS and CT	Rifampin appears to dramatically decrease the serum clindamycin concentration.	Serum clindamycin levels and effectiveness should be carefully monitored. A clinically relevant effect of clindamycin on rifampin concentrations is not expected.

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

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

9.7 Drug-Laboratory Test Interactions

Interactions between clindamycin and laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Following parenteral administration, biologically inactive clindamycin injection is rapidly hydrolyzed in plasma to active clindamycin. Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis. It binds to the 50S ribosomal subunit and affects both ribosome assembly and the translation process. At usual doses, clindamycin exhibits bacteriostatic activity in vitro.

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.

10.2 Pharmacodynamics

(see 15 MICROBIOLOGY).

10.3 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 7 records tissue and body fluid levels of clindamycin base following administration of clindamycin injection in adult patients undergoing surgical procedures.

Table 7. Clindamycin concentrations in Tissues and Fluids

Specimen	Dosage of clindamycin injection	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 8. Average Peak Serum Concentrations after Dosing with Clindamycin Phosphate

Clindamycin Phosphate Dosage Regimen	Clindamycin mcg/mL	Clindamycin Phosphate 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.

Elimination:
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 injection 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).

- **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).

- **Obese Pediatric Patients Aged 2 to Less than 18 Years and Obese Adults Aged 18 to 20 Years:** An analysis of pharmacokinetic data in obese pediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years demonstrated that clindamycin clearance and volume of distribution normalized by total body weight are comparable regardless of obesity.

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Clindamycin phosphate

Chemical Name:

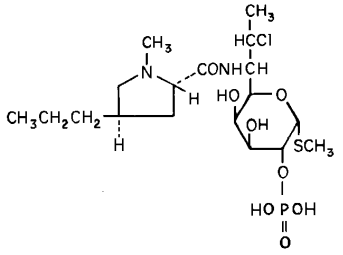
1) L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl) carbonyl] amino]-1-thio, 2-(dihydrogen phosphate), (2S-trans);

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

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

Molecular formula and molecular mass: $C_{18}H_{34}ClN_2O_8PS$, 505 g/mol

Structural Formula:



Physicochemical properties:
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.

14 CLINICAL TRIALS

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

15 MICROBIOLOGY

Efficacy is related to the time period over which the agent level is above the minimum inhibitory concentration (MIC) of the pathogen (%T/MIC).

Resistance

Resistance to clindamycin is most often due to mutations at the rRNA antibiotic binding site or methylation of specific nucleotides in the 23S RNA of the 50S ribosomal subunit. These alterations can determine in vitro cross resistance to macrolides and streptogramins B (MLSB phenotype). Resistance is occasionally due to alterations in ribosomal proteins. Resistance to clindamycin may be inducible by macrolides in macrolide-resistant bacterial isolates. Inducible resistance can be demonstrated with a disk test (D-zone test) or in broth. Less frequently encountered resistance mechanisms involve modification of the antibiotic and active efflux. There is complete cross resistance between clindamycin and lincomycin. As with many antibiotics, the incidence of resistance varies with the bacterial species and the geographical area. The incidence of resistance to clindamycin is higher among methicillin-resistant staphylococcal isolates and penicillin-resistant pneumococcal isolates than among organisms susceptible to these agents.

Breakpoints

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.
Particularly in severe infections or therapy failure microbiological diagnosis with verification of the pathogen and its susceptibility to clindamycin is recommended.

Resistance is usually defined by susceptibility interpretive criteria (breakpoints) established by Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) for systemically administered antibiotics.

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 9 identifies the currently-accepted NCCLS (1990) MIC interpretative breakpoints for clindamycin.

Clinical and Laboratory Standards Institute (CLSI) breakpoints for relevant organisms are listed below.

Table 9. CLSI Susceptibility Interpretive Criteria for Clindamycin

Pathogen	Minimal Inhibitory Concentrations (MIC in mcg/mL)			Disk Diffusion (Zone Diameters in mm) [a]		
Staphylococcus spp.	S ≤0.5	I 1-2	R ≥4	S ≥21	I 15-20	R ≤14
Streptococcus pneumoniae and other *Streptococcus spp.*	≤0.25	0.5	≥1	≥19	16-18	≤15
Anaerobic Bacteria[b]	≤2	4	≥8	NA	NA	NA

NA = not applicable

[a]Disk content 2 micrograms of clindamycin

[b]MIC ranges for anaerobes are based on agar dilution methodology

A report of "Susceptible" (S) indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" (I) indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant"(R) indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the usually achievable concentrations; other therapy should be selected.

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 MIC90 value was calculated to account for differences in the number of strains in each study.

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard clindamycin powder should provide the MIC ranges in Table 10. For the disk diffusion technique using the 2 mcg clindamycin disk the criteria provided in Table 10 should be achieved.

Table 10. CLSI Acceptable Quality Control (QC) Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	Minimum Inhibitory Concentration Range (mcg/mL)	Disk Diffusion Range (Zone Diameters in mm)
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619	0.03–0.12	19–25
Bacteroides fragilis ATCC 25285	0.5–2[a]	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8[a]	NA
Eggerthella lenta ATCC 43055	0.06–0.25[a]	NA

NA=Not applicable.

ATCC® is a registered trademark of the American Type Culture Collection

[a]MIC ranges for anaerobes are based on agar dilution methodology.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are presented below.

Table 11. EUCAST Susceptibility Interpretive Criteria for Clindamycin

	MIC breakpoints (mg/L)		Zone diameter breakpoints (mm)[a]	
Organism	**S ≤**	**R >**	**S ≥**	**R <**
Staphylococcus spp.	0.25	0.5	22	19
Streptococcus Groups A, B, C and G	0.5	0.5	17	17
Streptococcus pneumoniae	0.5	0.5	19	19
Viridans group streptococci	0.5	0.5	19	19
Gram-positive anaerobes	4	4	NA	NA
Gram-negative anaerobes	4	4	NA	NA
Corynebacterium	0.5	0.5	20	20

spp.				
[a]Disk content 2 mcg of clindamycin NA=not applicable; S=susceptible; R=resistant				

EUCAST QC ranges for MIC and disk zone determinations are in the table below.

Table 12. EUCAST Acceptable Quality Control (QC) Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	Minimum Inhibitory Concentration Range (mcg/mL)	Disk Diffusion Range (Zone Diameters in mm)
Staphylococcus aureus ATCC 29213	0.06–0.25	23-29
Streptococcus pneumoniae ATCC 49619	0.03–0.125	22-28

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The in vitro susceptibility of clinical isolates to clindamycin is presented in Table 13 (gram-positive aerobic bacteria), Table 14 (gram-negative aerobic bacteria), Table 15 (gram-positive anaerobic bacteria), Table 16 (gram-negative anaerobic bacteria) and Table 17 (*Chlamydia* spp and *Mycoplasma* spp).

Table 13. 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 MIC_{90} values
d MIC_{90} for single study or weighted average MIC_{90} for two or more studies

Table 14. 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
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 MIC_{90} values
d MIC_{90} for single study or weighted average MIC_{90} for two or more studies

Table 15. 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 16. In vitro activity of clindamycin against gram-negative anaerobic bacteria [a]

Organism	N[b]	MIC_{90} Range [c]	MIC_{90} [d]
Bacteroides fragilis group	4284	0.5-8	2.45
Bacteroides fragilis	2002	≤ 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 MIC_{90} 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 17). For Chlamydia trachomatis, the MIC90 for clindamycin is reached at 2.3 mcg/mL; in vitro synergism with gentamicin has also been demonstrated.

Table 17. 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 7600 isolates). Susceptibility of isolates to clindamycin should be assessed by individual MIC determinations.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity
The results of LD_{50} studies are shown in Table 18.

Table 18. LD_{50} Results

Species	Route	LD_{50} (mg/kg)
Adult Mouse	IP	1145
Adult Mouse	IV	855
Adult Rat	SC	> 2000
Adult Rat	PO	1832
Newborn Rat	SC	179

Tables 19 and 20 summarize toxicity and teratology studies. Table 21 summarizes human studies.

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

Table 19. TOXICITY STUDIES

Type of Study	Species	Route	Dose mg/kg/day	Duration	Conclusions
Tolerance	Rabbit N = 3	IM	100, 200, 300	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

Type of Study	Species	Route	Dose mg/kg/day	Duration	Conclusions
					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 injection 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 20. 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 21. HUMAN TOLERANCE STUDIES

N	Route	Dose	Duration	Conclusions
8	IM	300 mg clindamycin injection	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 injection	Single dose	Only three patients had short-lived moderate pain 30 minutes after injection.
24	IM	Group 1 (8 patients): 300 mg clindamycin injection Group 2 (8 patients): 2 mL of sodium chloride injection USP Group 3 (8 patients): 600 mg Lincocin sterile solution	Every 8 hr (total 43 injections)	One volunteer in each of the clindamycin injection 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

N	Route	Dose	Duration	Conclusions
				suspected viral illness; one due to a rash and one because of headache and tinnitus. In general, in these small groups, clindamycin injection was as well tolerated as Lincocin. There was no necrosis in any case. Pain, tenderness, swelling and induration were typically mild. Two clindamycin injection-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 injection and Lincocin groups. SGOT also rose above normal in the clindamycin group, but not in the

<table>
<tr><th>N</th><th>Route</th><th>Dose</th><th>Duration</th><th>Conclusions</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Lincocin group. SGPT findings remained within normal range in all groups. These changes are consistent with changes due to muscle irritation and not attributed to liver damage.</td></tr>
<tr><td>20</td><td>IV</td><td>Dosing Schedule
<table>
<tr><th>Subject Nos.</th><th>Treatment Group</th><th>Dose (mg)</th><th>Infusion Regimen</th><th>Infusion Rate</th><th>Total Daily Dose (mg)</th></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></td><td>Five days</td><td>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</td></tr>
</table>

N	Route	Dose						Duration	Conclusions
									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 injection

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

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

Reproductive and Developmental Toxicology:
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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. DALACIN C PHOSPHATE (Solution, 150 mg/mL), submission control 255973, Product Monograph, Pfizer Canada ULC. (January 10, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] CLINDAMYCIN INJECTION USP
Clindamycin Injection

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 is Clindamycin Injection USP 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 proteins 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:
Preservative-free Formulation: disodium edetate, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.

Multidose Formulation (benzyl alcohol-preserved): benzyl alcohol, disodium edetate, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.

Clindamycin Injection USP comes in the following dosage forms:
Preservative-free Formulation:
2 mL, 4 mL and 6 mL single-use glass vials, in boxes of 10.

Pharmacy Bulk Vial: 60 mL.

Multidose Formulation (benzyl alcohol-preserved):
2 mL, 4 mL and 6 mL multidose glass vials, in boxes of 10.

Pharmacy Bulk Vial: 60 mL.

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. Clindamycin passes to the human fetus
- are breastfeeding or planning to breastfeed.
- you are taking primaquine for an enzyme deficiency called glucose-6-phosphate dehydrogenase (G-6-PD). You need to have routine blood tests, to monitor for potential blood cell changes.

Other warnings you should know about:
Multidose Formulation of Clindamycin Injection USP contains benzyl alcohol which may be harmful to newborns and children up to 3 years old.

Breastfeeding
If you are breastfeeding or planning to breastfeed while taking Clindamycin Injection USP, talk to your doctor. Clindamycin Injection USP will pass through your breast milk to your baby. Your doctor will decide if you should take this medicine while breastfeeding. If your doctor has told you that you can take Clindamycin Injection USP while breastfeeding, monitor your baby for possible side effects such as: diarrhea, mouth infection (thrush: white lesions in your baby's mouth), diaper rash or blood in their stool. If your baby shows any signs, talk to your doctor and to your baby's doctor.

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)
- Rifampin (an antibiotic)
- Muscle relaxants used during operations
- Primaquine (antimalarial)
- Aminoglycosides (a class of antibiotics)
- St-John's Wort (Hypericum perforatum)

Tell your doctor if you are taking or being administered any other topical or oral medication, including erythromycin or neuromuscular blocking agents.

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, or a person you are caring for, have taken too much Clindamycin Injection USP, contact a 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			
Acute kidney failure (severe			√

kidney problems): confusion; tiredness; swelling; urinating less or not at all; shortness of breath; chest pain, seizures, coma			
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, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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:

- This medicine should be stored at room temperature (15 to 30°C).
- This medicine should not be refrigerated or frozen.

Keep out of the reach and sight of children.

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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