PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Clindamycin Injection in 5% Dextrose

Ready-to-use bags, clindamycin 6 mg / mL (300 mg / 50 mL), 12 mg / mL (600 mg / 50 mL) and 18 mg / mL (900 mg / 50 mL) (as clindamycin phosphate)

Sterile solution

Antibiotic

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[Pr]Clindamycin Injection in 5% Dextrose
(as clindamycin phosphate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous (IV)	Solution, clindamycin 6 mg/mL, 12 mg/mL, 18 mg/mL (as clindamycin phosphate)	None. *For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

Clindamycin Injection in 5% Dextrose (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 in 5% Dextrose (clindamycin phosphate) 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 in 5% Dextrose (clindamycin phosphate) 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 in 5% Dextrose (clindamycin phosphate) 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 in 5% Dextrose and other antibacterial drugs, Clindamycin Injection in 5% Dextrose 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)
Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients.

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 (See WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics (≥ 65 years), DOSAGE AND ADMINISTRATION, Geriatrics (≥ 65 years)).

Pediatrics (≤ 12 years)
It is not known if use of clindamycin in the pediatric population is associated with differences in safety or effectiveness compared with adult patients.

Clindamycin Injection in 5% Dextrose GALAXY plastic containers are not suitable for use in pediatric patients. Pediatric dosing requires dose adjustments which would result in partial use of the GALAXY plastic containers. Partial use of GALAXY plastic containers is not feasible in a clinical setting, therefore clindamycin injection (150 mg / mL) is more suitable for dosing in this population (See WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (≤ 12 years); DOSAGE AND ADMINISTRATION, Pediatrics (≤ 12 years)).

CONTRAINDICATIONS

Clindamycin Injection in 5% Dextrose (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 container (for a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph).

WARNINGS AND PRECAUTIONS

General
The partial use of clindamycin phosphate GALAXY plastic containers is not recommended.

Clindamycin Injection in 5% Dextrose does not diffuse adequately into cerebrospinal fluid and thus should not be used in the treatment of meningitis.

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 in 5% Dextrose (clindamycin phosphate) should be prescribed with caution in atopic individuals and 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).

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 ADVERSE REACTIONS and DRUG INTERACTIONS).

If patients should develop serious hematologic adverse effects, reducing the dosage regimen of primaquine and/or Clindamycin Injection in 5% Dextrose should be considered (see 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 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 in 5% Dextrose 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. Periodic kidney function tests and blood counts should be performed during prolonged therapy.

Susceptibility/Resistance

Prescribing Clindamycin Injection in 5% Dextrose 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.

Skin

Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported reactions.

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.

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 (≤ 12 years): Clindamycin Injection in 5% Dextrose GALAXY plastic containers are not suitable for use in pediatric patients. Pediatric dosing requires dose adjustments which would result in partial use of the GALAXY plastic containers. Partial use of GALAXY plastic containers is not feasible in a clinical setting, therefore clindamycin injection (150 mg/mL) is more suitable for dosing in this population. (See WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (≤ 12 years); DOSAGE AND ADMINISTRATION, Pediatrics (≤ 12 years)).

Geriatrics (≥ 65 years): Experience has demonstrated that antibiotic-associated colitis may occur more frequently and with increased severity among elderly (> 65 years) and debilitated patients. 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 (see DOSAGE AND ADMINISTRATION, Geriatrics (≥ 65 years)).

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.

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 Injection phosphate 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 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).

Primaquine
In patients with G-6-PD deficiency, the combination of clindamycin with primaquine may result in hemolytic reactions (see WARNINGS AND PRECAUTIONS). Serious hematologic toxicities (grade III, grade IV neutropenia or anemia, platelet counts $< 50 \times 10^9$/L, or methemoglobin levels of 15% or greater) have been observed. Routine blood examinations should be done during therapy with primaquine to monitor potential hematologic toxicities.

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 in 5% Dextrose dose modification may not be necessary in patients with renal disease. Clindamycin Injection in 5% Dextrose 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.

NOTE: If diarrhea occurs during treatment, this antibiotic should be discontinued (see WARNINGS AND PRECAUTIONS).

The partial use of clindamycin phosphate GALAXY plastic containers is not recommended.

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.

As with all parenteral products, the intravenous mixture should be inspected visually for clarity, discolouration, particulate matter, precipitate and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Recommended Dose and Dosage Adjustment

Adults (IV Administration)

The usual daily adult dosage of Clindamycin Injection in 5% Dextrose (clindamycin phosphate) for infections of the intra-abdominal area, female pelvis, and other complicated or serious infections is 2400-2700 mg given in 3 or 4 equal doses. Less complicated infections may respond to lower doses such as 1200- 1800 mg/day administered in 2 or 3 equal doses.

Pelvic Inflammatory Disease

Clindamycin Injection in 5% Dextrose 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 in 5% Dextrose 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 in 5% Dextrose should be considered.

Infusion Rates

Infusion rates for Clindamycin Injection in 5% Dextrose should NOT EXCEED 30 MG PER MINUTE as indicated below:

Dose	Strength	Time
300 mg/50 mL	6 mg/mL	10 min.
600 mg/50 mL	12 mg/mL	20 min.
900 mg/50 mL	18 mg/mL	30 min.

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:

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.

Pediatrics (≤ 12 years)
Clindamycin Injection in 5% Dextrose GALAXY plastic containers are not suitable for use in pediatric patients. Pediatric dosing requires dose adjustments which would result in partial use of the GALAXY plastic containers. Partial use of GALAXY plastic containers is not feasible in a clinical setting, therefore clindamycin injection (150 mg/mL) is more suitable for dosing in this population (See INDICATIONS AND CLINICAL USE, Pediatrics (≤12 years)).

Geriatrics (≥ 65 years)
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.

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. Doses of up to 4800 mg daily have been used without adverse effects.

For management of suspected overdosage, contact your regional Poison Control Centre immediately.

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

Table 3: 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 4: 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

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

Exposure of pharmaceutical products to heat should be minimized. It is recommended that Clindamycin Injection in 5% Dextrose in GALAXY plastic container be stored between 15°C to 25°C. Avoid temperatures above 30°C.

SPECIAL HANDLING INSTRUCTIONS

All parenteral products should be visually inspected for haziness, particulate matter, discolouration and leakage prior to administration.

Premixed Clindamycin Injection in 5% Dextrose is for intravenous infusion using sterile equipment. Check for minute leaks prior to use by squeezing bag firmly. If leaks are found, discard solution as sterility may be impaired. Do **NOT** add supplementary medication.

Do **NOT** use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach the GALAXY bag to the administration set. Refer to complete directions accompanying the administration set.

Compatibility with other products

Clindamycin has been shown to be compatible with gentamicin sulfate, tobramycin sulfate and

amikacin sulfate.

Incompatibility with other products
Clindamycin is physically incompatible with ampicillin, phenytoin sodium, barbiturates, aminophyllin, calcium gluconate, magnesium sulfate, ceftriaxone sodium, and ciprofloxacin. Following treatment with Clindamycin Injection in 5% Dextrose GALAXY plastic containers, the infusion line should be flushed with saline prior to IV administration of these drugs.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Clindamycin Injection in 5% Dextrose is a ready-to-use solution for IV administration.

300 mg/50 mL ready-to-use GALAXY plastic container
Each 50 mL of Clindamycin Injection in 5% Dextrose solution contains clindamycin phosphate equivalent to 300 mg of clindamycin, 2500 mg dextrose hydrous, 2 mg of edetate disodium dihydrate, hydrochloric acid and/or sodium hydroxide to adjust pH and water for injection.

600 mg/50 mL ready-to-use GALAXY plastic container
Each 50 mL of Clindamycin Injection in 5% Dextrose solution contains clindamycin phosphate equivalent to 600 mg of clindamycin, 2500 mg dextrose hydrous, 2 mg of edetate disodium dihydrate, hydrochloric acid and/or sodium hydroxide to adjust pH and water for injection.

900 mg/50 mL ready-to-use GALAXY plastic container
Each 50 mL of Clindamycin Injection in 5% Dextrose solution contains clindamycin phosphate equivalent to 900 mg of clindamycin, 2500 mg dextrose hydrous, 2 mg of edetate disodium dihydrate, hydrochloric acid and/or sodium hydroxide to adjust pH and water for injection.

Clindamycin Injection in 5% Dextrose is available in 50 mL GALAXY plastic containers in a case of 24.

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), (2*S*-*trans*);

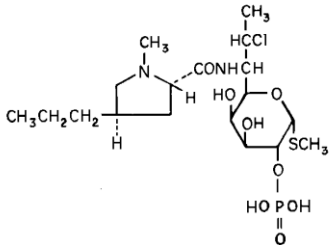
2) Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside 2-(dihydrogen phosphate);

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

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

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 phosphate.

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.

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 2). 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 3.7 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 5: 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 6, 7, 8 and 9**.**

Table 6: 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 7: 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
	0.5	1.5	3	6	12	24	(hrs)
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 8: 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 9: 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**
	0.5	**1.5**	**3**	**6**	**12**	**24**	**(hrs)**
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 10 by application of elimination half-lives (see Excretion).

Table 10: 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	

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations for most indicated organisms by administration of clindamycin phosphate in adults every 8 to 12 hours, 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 11 identifies the currently-accepted NCCLS (1990) MIC interpretative breakpoints for clindamycin.

Table 11: 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
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 12 (gram-positive aerobic bacteria), Table 13 (gram-negative aerobic bacteria), Table 14 (gram-positive anaerobic bacteria), Table 15 (gram-negative anaerobic bacteria) and Table 16 (*Chlamydia* spp and *Mycoplasma* spp).

Table 12: *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 pneumoniae (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

Table 12: *In vitro* activity of clindamycin against gram-positive aerobic bacteria [a]			
Organism	**N[b]**	**MIC_{90} Range [c]**	**MIC_{90} [d]**
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 13: *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 14: *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

Table 14: *In vitro* activity of clindamycin against gram-positive anaerobic bacteria [a]			
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 15: *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 13). For *Chlamydia trachomatis*, the MIC_{90} for clindamycin is reached at 2.3 mcg/mL; *in vitro* synergism with gentamicin has also been demonstrated.

Table 16: *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 (50*S* ribosomal subunit).

Resistance can result from either changes in a ribosomal protein at the receptor site or a change in the 23*S* 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.

TOXICOLOGY

Acute Toxicity

The results of LD_{50} studies are shown in Table 17:

Table 17: 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 18 and 19 summarize toxicity and teratology studies. Table 20 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 18: TOXICITY STUDIES

Type of Study	Species	Route	Dose mg/kg/d	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 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 19: 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 20: HUMAN TOLERANCE STUDIES

<table>
<tr><th>N</th><th>Route</th><th>Dose</th><th>Duration</th><th>Conclusions</th></tr>
<tr><td>8</td><td>IM</td><td>300 mg clindamycin phosphate</td><td>Single dose</td><td>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.</td></tr>
<tr><td>8</td><td>IM</td><td>600 mg clindamycin phosphate</td><td>Single dose</td><td>Only three patients had short-lived moderate pain 30 minutes after injection.</td></tr>
<tr><td>24</td><td>IM</td><td>Group 1 (8 patients): 300 mg clindamycin phosphate
Group 2 (8 patients): 2 mL of sodium chloride injection USP
Group 3 (8 patients): 600 mg Lincocin sterile solution</td><td>Every 8 hr. (total 43 injections)</td><td>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 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 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>
</table>

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

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PATIENT MEDICATION INFORMATION

[Pr]Clindamycin Injection in 5% Dextrose
(as clindamycin phosphate)

Read this carefully before you start taking Clindamycin Injection in 5% Dextrose and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Contact your doctor or pharmacist if you have any questions about the drug.

Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Clindamycin Injection in 5% Dextrose.

Antibacterial drugs like Clindamycin Injection in 5% Dextrose 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 in 5% Dextrose should be taken exactly as directed. Misuse or overuse of Clindamycin Injection in 5% Dextrose could lead to the growth of bacteria that will not be killed by Clindamycin Injection in 5% Dextrose. This means that Clindamycin Injection in 5% Dextrose may not work for you in the future.

What Clindamycin Injection in 5% Dextrose is used for?
Clindamycin Injection in 5% Dextrose is used for the treatment of serious bacterial infections

How does Clindamycin Injection in 5% Dextrose work?
Clindamycin Injection in 5% Dextrose reduces the production of key proteins in germs. This prevents growth in germs and reduces the infection.

What are the ingredients in Clindamycin Injection in 5% Dextrose?

Medicinal ingredients: Clindamycin phosphate

Nonmedicinal ingredients: Dextrose hydrous, edetate disodium dihydrate and water for injection. It may also contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

Clindamycin Injection in 5% Dextrose comes in the following dosage forms:
Clindamycin Injection in 5% Dextrose is available in ready-to-use 50 mL GALAXY plastic containers containing clindamycin premixed with 5% Dextrose w/v as a sterile solution.

Each 50 mL GALAXY plastic container contains clindamycin phosphate equivalent to 300 mg, 600 mg or 900 mg clindamycin. The single dose GALAXY plastic containers are available as follows:

300 mg/50 mL, case of 24
600 mg/50 mL, case of 24
900 mg/50 mL, case of 24

Clindamycin Injection in 5% Dextrose is for intravenous infusion only.

Do not use Clindamycin Injection in 5% Dextrose if:
You are allergic (hypersensitive) to:

- Clindamycin
- Lincomycin
- Other ingredients in the product (see list of nonmedicinal ingredients).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Clindamycin Injection in 5% Dextrose. 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. Clindamycin is passed to the infant through human breast milk. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be administered to nursing mothers.
- you have glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and are taking primaquine. You may need to have routine blood tests while taking Clindamycin Injection in 5% Dextrose with primaquine, to monitor for potential blood cell changes.

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 in 5% Dextrose:

- 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 in 5% Dextrose:
The health care professional will administer Clindamycin Injection in 5% Dextrose and will:

- Decide:
  - the dose and rate of administration of the medicine
- Ensure that:
  - the medicine will be given as an injection (infusion) through the vein
  - 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 in 5% Dextrose:
- If you have to use clindamycin 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.

This particular product format in GALAXY plastic container is not suitable for use in children 12 years of age and under.

Overdose:

If you think you have taken too much Clindamycin Injection in 5% Dextrose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Your healthcare professional will ensure that this product is administered each day and doses are not missed, as it works best when there is a constant amount in the body. If the medicine is stopped too soon, your symptoms may return. If you feel a dose has been missed contact your healthcare professional.

Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by clindamycin phosphate or other antibacterial drugs in the future

What are possible side effects from using Clindamycin Injection in 5% Dextrose?
These are not all the possible side effects you may feel when taking Clindamycin Injection in 5% Dextrose. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Clindamycin Injection in 5% Dextrose 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 or bleeding
- low white blood cells (neutropenia) which can lead to an increased chance of infections
- vaginal infection or vaginitis (inflamed vagina)

Contact your doctor immediately if the following happens:
- you have symptoms of a severe allergic reaction 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 symptoms of liver problems such as:
  - yellowing of the skin and whites of the eyes (jaundice).
- you have symptoms of *Clostridium difficile* colitis (bowel inflammation) such as:
  - severe, persistent, watery or bloody diarrhea with or without
    - fever
    - abdominal pain or tenderness 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 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:

The healthcare professional will store Clindamycin Injection in 5% Dextrose GALAXY plastic containers under appropriate conditions (15˚C to 25˚C). Avoid temperatures above 30°C.

Keep out of the reach and sight of children.

If you want more information about Clindamycin Injection in 5% Dextrose:

- 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.html); or by calling Baxter Corporation at: 1-888-719-9955

This leaflet was prepared by Baxter Corporation, Mississauga, Ontario L5N 0C2, Canada.

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