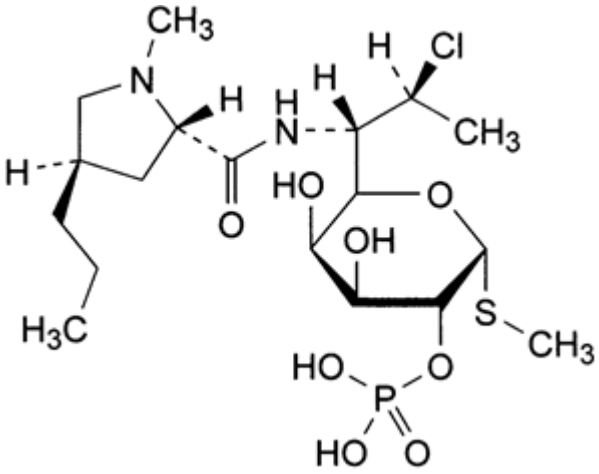
PRODUCT INFORMATION

CLINDAMYCIN MYLAN
Solution for Injection

Clindamycin phosphate

NAME OF THE MEDICINE

Active ingredient	:	Clindamycin phosphate
Chemical name	:	Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-L-threo-α-D-galacto-octopyranoside 2-(dihydrogen phosphate)
Structural formula	:	

Molecular formula	:	$C_{18}H_{34}ClN_2O_8PS$	Molecular weight	:	504.96
			CAS Registry no.	:	24729-96-2

DESCRIPTION

Clindamycin phosphate injection is a sterile solution of a water soluble ester of clindamycin and phosphoric acid which contains the equivalent of 150 mg clindamycin base and 0.5 mg disodium edetate in each mL of water for injections. Clindamycin is a semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin. The pH of the injection is 5.5 – 7.0.

PHARMACOLOGY

Microbiology

Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

Aerobic gram-positive cocci, including:

Staphylococcus aureus

Staphylococcus epidermidis (penicillinase and non-penicillinase producing strains)

When tested by *in vitro* methods some staphylococcal strains, originally resistant to erythromycin, rapidly develop resistance to clindamycin.

Streptococci (not Enterococcus faecalis)

Pneumococci

Anaerobic gram-negative bacilli, including:
Bacteroides species
Fusobacterium species

Anaerobic gram-positive non-spore forming bacilli, including:
Propionibacterium
Eubacterium
Actinomyces species

Anaerobic and microaerophilic gram-positive cocci, including:
Peptococcus species
Peptostreptococcus species
Microaerophilic *streptococci*
Clostridia
Clostridia are more resistant than most anaerobes to clindamycin. Most *C. perfringens* are susceptible, but other species, e.g. *C. sporogenes* and *C. tertium* are frequently resistant to clindamycin.

Susceptibility testing should be done.

Cross-resistance has been demonstrated between clindamycin and lincomycin.

Disc Susceptibility Testing

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility testing procedures require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures.

A report of "Susceptible" 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" 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, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable and other therapy should be selected.

The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Biologically inactive clindamycin phosphate is rapidly converted to active clindamycin.

By the end of short-term intravenous infusion, peak serum levels of active clindamycin are reached.

In vitro studies *i*n human liver and intestinal microsomes indicated that clindamycin is predominately oxidized by CYP3A4, with minor contribution for CYP3A5, to from clindamycin sulfoxide and a minor metabolite, N-desmethylclindamycin.

Biologically-inactive clindamycin phosphate disappears rapidly from the serum, the average disappearance half-life is 6 minutes; however, the serum disappearance half-life of active clindamycin is about 3 hours in adults and 2.5 hours in children.

After intramuscular injection of clindamycin phosphate, peak levels of active clindamycin are reached within 3 hours in adults and 1 hour in children. Serum level curves may be constructed from IV peak serum levels as given in Table 1 by application of the disappearance half-lives listed above.

Serum levels of clindamycin can be maintained above the *in vitro* minimum inhibitory concentrations for most indicated organisms by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in children, or by continuous intravenous infusion. An equilibrium state is reached by the third dose.

The disappearance half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function; dosage schedules need not be modified in the presence of mild to moderate renal or hepatic disease. No significant levels of clindamycin are attained in the cerebrospinal fluid even in the presence of inflamed meninges.

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

Table 1: Average Peak Serum Concentrations After Dosing with clindamycin phosphate

Dosage Regimen	Clindamycin (micrograms/mL)	Clindamycin Phosphate (micrograms/mL)
Healthy Adult Males (Post Equilibrium)		
300 mg IV in 10 min q 8 h	7	15
600 mg IV in 20 min q 8 h	10	23
900 mg IV in 30 min q 12 h	11	29
1200 mg IV in 45 min q 12 h	14	49
300 mg IM q 8 h	6	3
600 mg IM q 12 h*	9	3
Children (first dose)*		
5-7 mg/kg in 1 h	10	
3-5 mg/kg IM	4	
5-7 mg/kg IM	8	

*Data in this group from patients being treated for infection

INDICATIONS

CLINDAMYCIN MYLAN is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

CLINDAMYCIN MYLAN is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci and staphylococci.

Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgement of the physician, a penicillin is inappropriate.

Anaerobes

Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and skin structure infections; septicaemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract) and infections of the female pelvis and genital tract such as endometritis, non-gonococcal tubo-ovarian abscess, pelvic cellulitis and post-surgical vaginal cuff infection, all when given in conjunction with an antibiotic of appropriate gram-negative aerobic spectrum.

Streptococci

Serious respiratory tract infections; serious skin and skin structure infections; septicaemia.

Staphylococci

Serious respiratory tract infections; serious skin and skin structure infections; septicaemia; acute haematogenous osteomyelitis.

Pneumococci

Serious respiratory tract infections.

Adjunctive Therapy

In the surgical treatment of chronic bone and joint infections due to susceptible organisms.

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

CONTRAINDICATIONS

This drug is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin, lincomycin or any of the ingredients listed under **DESCRIPTION.**

PRECAUTIONS

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE. OXYGEN, COLLOID INFUSION, ANTIHISTAMINES AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

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

The use of clindamycin can lead to the development of severe colitis. Fatalities have been reported. Therefore, clindamycin should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the **INDICATIONS** section. It should not be used in patients with non-bacterial infections such as most upper respiratory tract infections.

A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with the use of antibiotics, including parenteral clindamycin. Symptoms may occur up to several weeks after cessation of antibiotic therapy.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone, however in moderate to severe cases appropriate therapy with suitable oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Antibiotic-associated colitis and diarrhoea (due to *C. difficile*), occur more frequently and may be more severe in debilitated and/or elderly patients (> 60 years). When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Clindamycin should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Clindamycin should be used with caution in patients with a history of regional enteritis, ulcerative colitis or antibiotic associated colitis.

Clindamycin should be prescribed with caution in atopic individuals.

During prolonged therapy periodic liver and kidney function tests and blood counts should be performed.

Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe, metabolic aberrations should be dosed with caution, and serum clindamycin levels monitored during high-dose therapy.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy. The use of clindamycin may result in overgrowth of non-susceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in the **DOSAGE AND ADMINISTRATION** section. Drugs which delay peristalsis (e.g. opiates and diphenoxylate with atropine) may prolong and/or worsen the condition and should not be used.

Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration (see **DOSAGE AND ADMINISTRATION**).

Local irritation, pain, induration and sterile abscess have been reported after intramuscular injection and thrombophlebitis after intravenous infusion (see **ADVERSE EFFECTS**). Reactions can be minimised by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters.

Usage in Meningitis

Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

Use in Pregnancy - Category A

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal concentrations. Clindamycin should be used in pregnancy only if clearly needed.

Use in Lactation

Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 micrograms/mL. Therefore, it is not recommended for nursing mothers.

Usage in the Newborn and Infants

When clindamycin is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

INTERACTIONS WITH OTHER MEDICINES

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance these two drugs should not be administered concurrently.

In vitro studies of human liver and intestinal microsomes showed that clindamycin is metabolised predominately by CYP3A4, and to a lesser extent by 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 rifampicin, 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.

See Compatibility/Incompatibility section under **DOSAGE AND ADMINISTRATION** for physicochemical interactions.

ADVERSE EFFECTS

The adverse effects listed in the table below are presented by system organ class. Within each frequency category, the adverse effects are presented in the order of frequency and then by decreasing medical seriousness.

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10000 to <1/1000)**	**Frequency not known (cannot be estimated from available data)**
Infections and Infestations	Pseudomembranous colitis			Vaginal infection
Blood and lymphatic system disorders	Eosinophilia			Agranulocytosis, neutropenia, thrombocytopenia, leucopenia
Immune system Disorders				Anaphylactoid reaction
Nervous system Disorders		Dysgeusia		
Cardiac Disorders		Cardiorespiratory arrest§†		
Vascular Disorders	Thrombophlebitis†	Hypotension§†		
Gastrointestinal Disorders	Diarrhoea, abdominal pain	Vomiting, Nausea		
Hepatobiliary disorders				Jaundice
Skin and Subcutaneous tissue disorders	Rash maculopapular	Urticaria	Erythema Multiforme, pruritus	Toxic epidermal necrolysis (TEN), Steven Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis, exfoliative, dermatitis bullous, rash morbilliform
Musculoskeletal and connective tissue disorders				Polyarthritis
General disorders and administration site conditions		Pain†, injection†		Injection site irritation†
Investigations	Liver function test abnormal			

CIOMS III categories: Very Common ≥1/10 (≥10%); Common ≥1/100 to <1/10 (≥1% and <10%); Uncommon ≥1/1000 to <1/100 (≥0.1% and <1%); Rare ≥1/10,000 to <1/1000 (≥0.01% and <0.1%); Very Rare <1/10,000 (<0.01%)

†Adverse reactions apply only to injectable formulations.
§Rare instances have been reported following too rapid intravenous administration (see **DOSAGE AND ADMINISTRATION).**

Post-Marketing Experience

The following additional adverse reactions have been reported during post-marketing experience.

Infections and infestations

Not known: *Clostridium difficile* colitis.

Immune system disorders

Not known: Anaphylactic shock, anaphylactic reaction, hypersensitivity.

Skin and subcutaneous tissue disorders

Not known: Angioedema

DOSAGE AND ADMINISTRATION

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 micro-organism.

Clindamycin Mylan IM administration should be used undiluted.

Clindamycin Mylan IV administration should be diluted (see Dilution for IV use and IV infusion rates below).

Product is for single use in one patient only. Discard any residue.

Adults (IM or IV Administration)

The usual daily adult dosage of clindamycin phosphate for infections of the intra-abdominal area, female pelvis and other complicated or serious infections is 1200 - 2700 mg given in 2, 3 or 4 equal doses. Doses of up to 4800 mg daily have been used successfully. Less complicated infections due to more susceptible organisms may respond to lower doses such as 600-1200 mg/day administered in 3 or 4 equal doses.

Single IM doses of greater than 600 mg are not recommended.

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

Serious infections: 15-25 mg/kg/day in 3 or 4 equal doses

More severe infections: 25-40 mg/kg/day in 3 or 4 equal doses

As an alternative to dosing on a body weight basis, children may be dosed on the basis of square metres of body surface.

Serious infections: 350 mg/m2/day

More severe infections: 450 mg/m2/day

In severe infections it is recommended that children be given no less than 300 mg per day regardless of body weight.

Parenteral therapy may be changed to oral clindamycin when the condition warrants and at the discretion of the physician.

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

Dilution for IV use and IV Infusion Rates

CLINDAMYCIN MYLAN must be diluted prior to IV administration. The concentration of clindamycin in diluent for infusion should not exceed 12 mg per mL AND INFUSED AT A RATE OF NOT MORE THAN 30 MG PER MINUTE AS INDICATED BELOW:

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 to 8^0C for not more than 24 hours.

Table 2: Dilution and Infusion Rates in Relation to Total Infusion Dose

Dose	Diluent	Minimum Time
300 mg	50 mL	10 min
600 mg	50 mL	20 min
900 mg	100 mL	30 min
1200 mg	100 mL	40 min

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

Compatibility/Incompatibility

Clindamycin has been known to be physically and chemically compatible for at least 24 hours in glucose 5% water and sodium chloride injection solutions containing the following antibiotics in usually administered concentrations: amikacin sulfate, aztreonam, cephamandole nafate, cephazolin sodium, cefotaxime sodium, cefoxitin sodium, ceftazidime sodium, ceftizoxime sodium, gentamicin sulfate, netilmicin sulfate, piperacillin and tobramycin. The compatibility and duration of stability of drug mixtures will vary depending on concentration and other conditions.

No incompatibility has been demonstrated with the antibiotics cephalothin, kanamycin, gentamicin, penicillin or carbenicillin.

The following drugs are physically incompatible with clindamycin: ampicillin, phenytoin sodium, barbiturates, aminophylline, calcium gluconate, magnesium sulfate, ceftriaxone sodium and ciprofloxacin.

OVERDOSAGE

The minimal toxic or lethal dose is not well established. At therapeutic doses, the primary toxic effects may involve the gastrointestinal tract and may include severe diarrhoea and pseudomembranous colitis that may result in death. Rapid administration of large doses has resulted in ventricular dysrhythmias, hypotension and cardiac arrest. Dermatitis, nephrotoxicity, hepatotoxicity, and various haematological abnormalities are toxic effects that occur less frequently.

No specific antidote is known. Support respiratory and cardiac function. In cases of overdose, drug levels of clindamycin are not clinically useful. However, monitoring serum concentrations in patients with markedly reduced renal and hepatic function, may be indicated during high-dose therapy. Monitor full blood count in patients with significant exposure as clindamycin may produce abnormalities of the haematopoietic system. Because clindamycin may cause hepatotoxicity, monitor liver function tests in patients with significant exposure.

Neither haemodialysis nor peritoneal dialysis appear to be effective in reducing clindamycin levels significantly.

Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen and intravenous corticosteroids should also be administered as indicated.

For information on the management of overdosage, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Each 1 mL of CLINDAMYCIN MYLAN solution for injection contains clindamycin phosphate equivalent to 150 mg clindamycin base; 0.5 mg disodium edetate; and Water for Injections q.s. When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid. This preparation is preservative free.

The following sizes are available:

CLINDAMYCIN Mylan 300mg/2 mL	:	Each clear glass vial contains 300 mg of clindamycin as the active ingredient, presented as a solution for injection Pack size 10 x 2 mL vials per carton. Store below 25ºC. Do not freeze.
CLINDAMYCIN Mylan 600mg/4 mL	:	Each clear glass vial contains 600 mg of clindamycin as the active ingredient, presented as a solution for injection Pack size 10 x 4 mL vials per carton. Store below 25ºC. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

6th June 2012

DATE OF MOST RECENT AMENDMENT

9th November 2017

CLINDAMYCIN MYLAN_pi\Sep/Ver01