℞ *For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.*

Clindamycin Injection IP 150 mg/ml

CLINDYM® 300/600

Each ml contains:

Clindamycin Phosphate IP eq. to Clindamycin	150 mg
Benzyl Alcohol IP (As Preservative)	9.45 mg
Water for Injection IP	q.s.

DESCRIPTION:
Clindamycin Phosphate is indicated in the treatment of serious infections. Clindamycin Phosphate is designated as 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-actopyranoside 2- (dihydrogen phosphate). It has a molecular weight of 505.0 g/mol and its molecular formula is $C_{18}H_{34}ClN_2O_8PS$.

THERAPEUTIC INDICATIONS:
Clindamycin Injection is indicated in the treatment of serious infections caused by susceptible Gram-positive organisms, staphylococci (both penicillinase- and non-penicillinase-producing), streptococci (except Streptococcus faecalis) and pneumococci. It is also indicated in serious infections caused by susceptible anaerobic pathogens such as Bacteroides spp., Fusobacterium spp., Propionibacterium spp., Peptostreptococcus spp. and microaerophilic streptococci.
Clindamycin does not penetrate the blood/brain barrier in therapeutically effective quantities.

POSOLOGY AND METHOD OF ADMINISTRATION
Parenteral (IM or IV administration). – 'see Method of administration' below
Adults: Serious infections: 600mg-1.2g/day in two, three or four equal doses.
More severe infections: 1.2-2.7g/day in two, three or four equal doses.
A single I.M. injection of greater than 600mg are not recommended nor is administration of more than 1.2g in a single one-hour infusion.
For more serious infections, these doses may have to be increased. In life-threatening situations, doses as high as 4.8g daily have been given intravenously to adults.
Alternatively, the drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion.
Paediatric population (over 1 month of age): Serious infections: 15-25mg/kg/day in three or four equal doses. More severe infections: 25-40mg/kg/day in three or four equal doses. In severe infections it is recommended that children be given no less than 300mg/day regardless of body weight.
Elderly patients: The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate are not altered by increased age. Analysis of data from clinical studies has not revealed any age-related increase in toxicity. Dosage requirements in elderly patients should not be influenced, therefore, by age alone.
Dosage in renal/hepatic impairment: clindamycin dosage modification is not necessary in patients with renal or hepatic insufficiency
Treatment for infections caused by beta-haemolytic streptococci should be continued for at least 10 days to guard against subsequent rheumatic fever or glomerulonephritis.
Method of administration
Parenteral (intramuscular or intravenous administration).
Clindamycin injection should be used undiluted for intramuscular administration.
Clindamycin injection must be diluted prior to intravenous administration and should be infused over at least 10 – 60 minutes.
Dilution for IV use and IV infusion rates
The concentration of clindamycin in diluent for infusion should not exceed 18mg per ml and Infusion Rates Should Not Exceed 30mg Per Minute. The usual infusion rates are as follows:

Dose	Diluent	Time
300mg	50ml	10 min
600mg	50ml	20 min
900mg	50ml -100ml	30 min
1200mg	100ml	40 min

CONTRAINDICATIONS:
Clindamycin Injection is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Warnings: 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 undesirable effects).
Clindamycin Injection should only be used in the treatment of serious infections. In considering the use of the product, the practitioner should bear in mind the type of infection and the potential hazard of the diarrhea which may develop, since cases of colitis have been reported during, or even two or three weeks following, the administration of clindamycin.
Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of Clostridium difficile. This has been reported with use of nearly all antibacterial agents, including clindamycin. Clostridium difficile produces toxins A and B which contribute to the development of Clostridium difficile associated diarrhoea (CDAD) and is a primary cause of 'antibiotic-associated colitis'.
The disease is likely to follow a more severe course in older patients or patients who are debilitated. Diagnosis is usually made by the recognition of the clinical symptoms, but can be substantiated by endoscopic demonstration of pseudomembranous colitis. Colitis is a disease which has a clinical spectrum from mild, watery diarrhoea to severe, persistent diarrhoea, leucocytosis, fever, severe abdominal cramps, which may be associated with the passage of blood and mucus. If allowed to progress, it may produce peritonitis, shock and toxic megacolon. This may be fatal. The presence of the disease may be further confirmed by culture of the stool for C. difficile on selective media and assay of the stool specimen for the toxin(s) of C. difficile.
It is important to consider the diagnosis of CDAD in patients who present with diarrhoea subsequent to the administration of antibacterial agents. This may progress to colitis, including pseudomembranous colitis, which may range from mild to fatal colitis. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including clindamycin, should be discontinued and adequate therapeutic measures should be initiated immediately. When 125 mg to 500 mg of vancomycin are administered orally four times a day for 7 - 10 days, there is a rapid observed disappearance of the toxin from faecal samples and a coincident clinical recovery from the diarrhoea. Drugs inhibiting peristalsis are contraindicated in this situation.
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.
Precautions: Caution should be used when prescribing Clindamycin Injection to individuals with a history of gastro-intestinal disease, especially colitis. Since clindamycin does not diffuse adequately into cerebrospinal fluid, the drug should not be used in the treatment of meningitis. If therapy is prolonged, liver and kidney function tests should be performed. Such monitoring is also recommended in neonates and infants. Safety and appropriate dosage in infants less than one month old have not been established. Acute kidney injury, including acute renal failure, has been reported infrequently. In patients suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs, monitoring of renal function should be considered (see undesirable effects). The use of clindamycin phosphate may result in overgrowth of non-susceptible organisms, particularly yeasts.
Prolonged administration of Clindamycin Injection, as with any anti-infective, may result in super-infection due to organisms resistant to clindamycin. Care should be observed in the use of Clindamycin Injection in atopic individuals. Clindamycin phosphate should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes (see posology and method of administration).

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. It should be used with caution, therefore, in patients receiving such agents.
Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.
Co-administration of clindamycin with inhibitors of CYP3A4 and CYP3A5 Clindamycin is metabolized predominantly by CYP3A4, and to a lesser extent by CYP3A5, to the major metabolite clindamycin sulfoxide and minor metabolite N desmethyl clindamycin. 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. Therefore, clinically important interactions between clindamycin and co-administered drugs metabolized by these CYP enzymes are unlikely

FERTILITY, PREGNANCY AND LACTATION:
Pregnancy: There was evidence of maternal toxicity and embryofetal toxicity in animal studies. Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal blood concentrations. Clindamycin should be used in pregnancy only if clearly needed.
Breast-feeding: Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from <0.5to 3.8 µg/mL. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. If oral or intravenous clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breastfed child from clindamycin or from the underlying maternal condition.
Fertility: Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Clindamycin has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS
Infections and Infestations:
Common: pseudomembranous colitis,
Not known: vaginal infection
Blood and Lymphatic System Disorders:
Not known: agranulocytosis, leukopenia, neutropenia, thrombocytopenia, eosinophilia
Immune System Disorders:
Not known: anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity
Nervous System Disorders:
Uncommon: dysgeusia
Cardiac Disorders:
Uncommon: cardiorespiratory arrest
Vascular Disorders:
Common: thrombophlebitis,
Uncommon: hypotension
Gastrointestinal Disorders:
Uncommon: diarrhoea, nausea,
Not known: abdominal pain, vomiting, oesophageal ulcers, oesophagitis jaundice
Skin and Subcutaneous Tissue Disorders:
Common: rash maculopapular,
Uncommon: urticaria erythema multiforme, pruritus,
Not known: toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptom (DRESS), acute generalized exanthematous pustulosis (AGEP), dermatitis exfoliative, dermatitis bullous, rash morbilliform.
General disorder and administrative conditions:
Uncommon: pain, injection site, abscess.
Investigations:
Common: liver function test abnormal.
Renal and urinary disorders:
Not known: acute kidney injury.

OVERDOSE:
In cases of overdosage no specific treatment is indicated. The serum biological half-life of lincomycin is 2.4 hours. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. If an allergic adverse reaction occurs, therapy should be with the usual emergency treatments, including corticosteroids, adrenaline and antihistamines.

PHARMACOLOGICAL PROPERTIES:
Pharmacotherapeutic group: Lincosamides
ATC code: J01FF01
Pharmacodynamic properties:
Mode of action
Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains. Although clindamycin phosphate is inactive in vitro, rapid in vivo hydrolysis converts this compound to the antibacterially active clindamycin.
Resistance
Resistance to Clindamycin usually occurs via macrolide-lincosamide-streptograminB (MLSB) type of resistance, which may be constitutive or inducible.
Breakpoints
The minimum inhibitory concentrations (MIC) breakpoints are as follows:
EUCAST
Staphylococci: sensitive ≤ 0.5 resistant > 0.5
Streptococci ABCG and pneumoniae: sensitive ≤ 0.5 resistant > 0.5
Gram positive anaerobes: sensitive ≤ 4 resistant > 4
Gram negative anaerobes: sensitive ≤ 4 resistant > 4
PK/PD relationship
Efficacy is related to the ratio of the area of the concentration-time curve of unbound antibiotic to the MIC for the pathogen (fAUC/MIC).

Pharmacokinetic properties:
General characteristics of active substance
Following parenteral administration, the biologically inactive clindamycin phosphate is hydrolysed to clindamycin. When the equivalent of 300mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 microgram/ml is achieved within three hours; 600mg gives a peak concentration of 9 microgram/ml. In children, peak concentration may be reached within one hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms per ml respectively are achieved by the end of infusion.
Distribution: Clindamycin is widely distributed in body fluids and tissues, including bone, but it does not reach the cerebrospinal fluid in significant concentrations. It diffuses across the placenta into the foetal circulation and appears in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90% of clindamycin in the circulation is bound to plasma proteins. The half-life is 2 to 3 hours, although this may be prolonged in pre-term neonates and patients with severe renal impairment.
Elimination: Clindamycin undergoes metabolism, to the active N-demethyl and Sulphoxide metabolites and also some inactive metabolites. About 10% of the drug is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Excretion is slow and takes place over several days. It is not effectively removed from the blood by dialysis.
Characteristics in patients: No special characteristics.

SPECIAL PRECAUTIONS FOR DISPOSAL
The product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2-8°C unless dilution has taken place in controlled and validated aseptic conditions.
The product should not be admixed with other drug products which are chemically or physically unstable at low pH. The compatibility and duration of stability of drug admixtures will vary depending upon concentration and other conditions.

STORAGE: Store below 30°C. Do not refrigerate, freeze.

PRESENTATION:
CLINDYM 300
Primary packing: 2 ml clear glass ampoule USP Type -I.
Secondary packing: Such one ampoule kept in a tray along with package insert packed in a monocarton.

CLINDYM 600
Primary packing: 4 ml clear glass ampoule USP Type -I.
Secondary packing: Such one ampoule kept in a tray along with package insert packed in a monocarton.

Marketed By:
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