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

Clindamycin Injection USP 150mg/ml

COMPOSITION

Each ml contains

Clindamycin Phosphate	USP	
Eq. to Clindamycin		150 mg
Benzyl Alcohol	USP	9.45mg
Water for Injection	USP	q.s.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Lincosamides

ATC code: J01FF01

Mechanism 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 the early stages of 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-streptogramin B (MLS_B) type of resistance, which may be constitutive or inducible.

Breakpoints

The minimum inhibitory concentrations (MIC) breakpoints are as follows:

EUCAST

Staphylococci: sensitive ≤ 0.25 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).

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Species
Susceptible
Gram-positive aerobes
Staphylococcus aureus *
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Viridans Streptococci
Anaerobes
Bacteriodes fragilis group
Prevotella formerly known as *Bacteroides melaninogenicus*
Bifidobacterium spp.
Clostridium perfringens
Eubacterium spp.
Fusobacterium spp.
Peptococcus spp.
Peptostreptococcus spp.
Propionibacterium spp.
Veillonella spp.
Resistant
Clostridia spp.
Enterococci
Enterobacteriaceae

***** Up to 50% of methicillin-susceptible *S. aureus* have been reported to be resistant to clindamycin in some areas. More than 90% of methicillin-resistant *S.aureus* (MRSA) are resistant to clindamycin and it should not be used while awaiting susceptibility test results if there is any suspicion of MRSA.

Most Gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin. Clindamycin demonstrates cross-resistance with lincomycin. When tested by in vitro methods, some staphylococcal strains originally resistant to erythromycin rapidly developed resistance to clindamycin. The mechanisms for resistance are the same as for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein and in a few staphylococcal isolates enzymic inactivation by a plasmid-mediated adenyltransferase

Pharmacokinetic properties

General characteristics of active substance

Absorption

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. In vitro studies in human liver and intestinal microsomes indicated that clindamycin is predominantly oxidized by CYP3A4, with minor contribution from CYP3A5, to form clindamycin sulfoxide and a minor metabolite, N- desmethylclindamycin. The half-life is 2 to 3 hours, although this may be prolonged in pre-term neonates and patients with severe renal impairment.

Biotransformation

Clindamycin undergoes metabolism, to the active *N*-demethyl and sulphoxide metabolites and also some inactive metabolites.

Elimination

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 warnings and special precautions for use"** for further information.

INDICATION AND USAGE

Antibacterial. 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.

Consideration should be given to official guidance on the appropriate use of antibacterial agents including national and local guidelines

CONTRA-INDICATION

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clindamycin 150mg/ml Solution for Injection and Infusion is contra-indicated in patients previously found to be sensitive to lincomycin

DRUG INTERACTIONS

Clindamycin administered by injection 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 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. Therefore, clinically important interactions between clindamycin and co-administered drugs metabolized by these CYP enzymes are unlikely.

WARNINGS AND PRECAUTIONS

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.

Clindamycin 150mg/ml Solution for Injection and Infusion 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 diarrhoea 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 150mg/ml Solution for Injection and Infusion to individuals with a history of gastro-intestinal disease, especially colitis.
Since Clindamycin 150mg/ml Solution for Injection and Infusion 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.
The use of Clindamycin 150mg/ml Solution for Injection and Infusion may result in the overgrowth of non-susceptible organisms particularly yeasts.
Prolonged administration of Clindamycin 150mg/ml Solution for Injection and Infusion, 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 150mg/ml Solution for Injection and Infusion in atopic individuals.
Clindamycin phosphate should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in section 4.2.
This medicine contains less than 1 mmol sodium (23 mg) per 2 ml ampoule, that is to say essentially 'sodium-free'.
This medicinal product contains 26 mg sodium per 4 ml ampoule, equivalent to 1.3% of the WHO recommended maximum daily intake of 2 g sodium for an adult."

SIDE EFFECTS
The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. The frequency of undesirable effects listed below is defined using the following convention:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Frequency	Undesirable effects
Infections and infestations	Common	pseudomembranous colitis*#
	Not Known	vaginal infection *
Blood and lymphatic system disorders	Not Known	agranulocytosis*, neutropenia*, thrombocytopenia*, leukopenia*, eosinophilia
Immune system disorders	Not Known	anaphylactic shock*, anaphylactoid reactions*, anaphylactic reaction*, hypersensitivity*
Nervous system disorders	Uncommon	dysgeusia
Cardiac disorders	Uncommon	cardio- respiratory arrest†§
Vascular Disorders	Common	thrombophlebitis†
	Uncommon	hypotension†§
Gastrointestinal disorders	Uncommon	diarrhoea, nausea,
	Not Known	Oesophageal ulcers, oesophagitis, , vomiting, abdominal pain
Hepatobiliary disorders	Not Known	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 generalised exanthematous pustulosis (AGEP)*, dermatitis exfoliative*, dermatitis bullous*, rash morbilliform*,
General disorders and administration site conditions	Uncommon	pain†, injection site abscess†
	Not Known	injection site irritation†*
Investigations	Common	liver function test abnormal

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

OVERDOSE
Management:
In cases of overdosage no specific treatment is indicated.
The serum biological half-life of Clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis.
If an allergic adverse reaction occurs, therapy should be with the usual emergency treatments, including corticosteroids, adrenaline and antihistamines.

DOSAGE & MODE OF ADMINISTRATION
Posology:
Adults:
Serious infections: 600 mg - 1.2 g/day in two, three or four equal doses.
More severe infections: 1.2 - 2.7 g/day in two, three or four equal doses.
Single IM injections of greater than 600 mg are not recommended nor is administration of more than 1.2 g 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 4.8 g 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 - 25 mg/kg bodyweight/day in three or four equal doses.
More severe infections: 25 - 40 mg/kg bodyweight/day in three or four equal doses. In severe infections it is recommended that children be given no less than 300 mg/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. Other factors which should be taken into consideration.
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 18 mg per mL and **infusion rates should not exceed 30mg per minute**. The usual infusion rates are as follows:

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

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.
In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.
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 0.7 to 3.8 µg/mL. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.
Fertility
Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability.

STORAGE CONDITION
Store at 20° to 25°C. Don't allow to freeze

KEEP OUT OF REACH OF CHILDREN

PRESENTATION
2ml Ampoule & 2ml, 4ml Single Dose Vials packed in cardboard carton along with pack insert.

MANUFACTURED IN INDIA
INDUS PHARMA PRIVATE LIMITED
5/2, Industrial Area, Kirti Nagar, New Delhi-110015
A WHO GMP Certified Company