1. NAME OF THE MEDICINAL PRODUCT

CEREMIT-150

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hard Gelatin Capsule contains

Clindamycin hydrochloride USP

Eq. to Clindamycin.....150 mg

Excipients .....Q.S.

Approved colors used in capsule shell

List of Excipients:

Excipients	Quantity /Capsule (mg)	Uses
SHIFTING/MIXING		
Maize Starch	97.100	Diluent
Dibasic Calcium Phosphate	30.00	Diluent
Purified Talc (Talcum)	5.00	Lubricant
Magnesium Stearate	5.00	Lubricant
Sodium Starch Glycolate	6.00	Disintegrants
Colloidal Anhydrous Silica (Colloidal Silicon Dioxide)	5.00	Adsorbent
FILLING		
E.H.G. CAPSULES SIZE 2 Red/White IH	64.00	Empty Capsules Shells

3. PHARMACEUTICAL FORM

A Red/White colored hard gelatin capsule size '2' containing white powder.

4. Clinical particulars

4.1 Therapeutic indications

Clindamycin is indicated for the treatment of:

Serious infections caused by anaerobic bacteria, including intra-abdominal infections, skin and soft tissue infections. As needed, clindamycin should be administered in conjunction with another antibacterial agent that is active against gram negative aerobic bacteria.

- Tonsillitis
- Dental infection

Consideration should be given to the official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method ofadministration

Posology

Adults

The usual dose is 150-450 mg every six hours, depending on the severity of the infection.

Elderly patients

Dosage requirements in elderly patients should not be influenced by age alone

Paediatric population

The usual dose is 3-6-mg/kg every six hours depending on the severity of the infection (not to exceed the adult dose).

Clindamycin capsules are not suitable for children who are unable to swallow them whole. The capsules do not provide exact mg/kg doses therefore it may be necessary to use an alternative formulation in some cases.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate impairment of renal function. In patients with severe renal impairment or anuria, plasma concentration should be monitored. Depending on the results, this measure can make a reduction in dosage or an increase in the dose interval of 8 or even 12 hours necessary.

Hepatic impairment

In patients with moderate to severe hepatic impairment, elimination half-life of clindamycin is prolonged. A reduction in dosage is generally not necessary if clindamycin is administered every 8 hours. However, the plasma concentration of clindamycin should be monitored in patients with severe hepatic impairment. Depending on the results, this measure can make a reduction in dosage or an increase in the dose intervals necessary.

Method of administration

Clindamycin capsules are given orally. The product should always be taken with a full glass of water in an upright position.

Absorption of Clindamycin capsules is not appreciably modified by the presence of food.

4.3 Special warnings and precautions for use

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 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.

Studies indicate a toxin(s) produced by clostridia (especially Clostridium difficile) is the principal direct cause of antibiotic-associated colitis. These studies also indicate that this toxigenic clostridium is usually sensitive in vitro to vancomycin. 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. (Where the patient is receiving cholestyramine in addition to vancomycin, consideration should be given to separating the times of administration).

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 mucous. If allowed to progress, it may produce peritonitis, shock and toxic megacolon. This may be fatal.

The appearance of marked diarrhoea should be regarded as an indication that the product should be discontinued immediately. 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. The presence of the disease may be further confirmed by culture of the stool for Clostridium difficile on selective media and assay of the stool specimen for the toxin(s) of C. difficile.

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.

Precautions: Caution should be used when prescribing Clindamycin capsules 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.

Laboratory tests for renal and hepatic function should be carried out during prolonged therapy.

Close monitoring is also recommended in patients with renal or hepatic insufficiency and in neonates and infants, all of whom may require dose reduction and/or an extended interval between doses.

Prolonged administration of Clindamycin capsules, 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 capsules in atopic individuals.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The choice of clindamycin should be based on factors such as severity of the infection, the prevalence of resistance to other suitable agents and the risk of selecting clindamycin-resistant bacteria

4.4 Interaction with other medicinal products and other forms of interaction

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.

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

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.

4.5 Pregnancy and Lactation

Pregnancy

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.

Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the foetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

Breast-feeding

Clindamycin is excreted in breast milk. 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

In animal studies, clindamycin had no effect on fertility or mating ability.

4.6 Effects on ability to drive and use machines

Clindamycin has no or negligible influence on the ability to drive and use machines.

4.7 Undesirable 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 grouping 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); and 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	Common ≥1/100 to < 1/10	Uncommon ≥1/1 000 to <1/100	Not Known (cannot be estimated from available data)
Infections and Infestations	pseudomembranous colitis*#		Clostridium difficile colitis*#, vaginal infection*
Blood and Lymphatic System Disorders			agranulocytosis*, neutropenia*,

			thrombocytopenia*, leukopenia*, eosinophilia
Immune System Disorders			anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*
Nervous System Disorders			dysgeusia
Gastrointestinal Disorders	diarrhoea, abdominal pain	Vomiting, nausea	oesophageal ulcer*, oesophagitis*
Hepatobiliary Disorders			jaundice*
Skin and Subcutaneous Tissue Disorders		rash maculopapular, urticaria	toxic epidermal necrolysis (TEN)*, Stevens Johnson syndrome (SJS)*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalized exanthematous pustulosis (AGEP*, angioedema*, dermatitis exfoliative*, dermatitis bullous*, erythema multiforme*, pruritus, rash morbilliform*
Investigations	Liver function test abnormal		

* ADR identified post-marketing.

See section 4.4.

4.8 Overdose

The serum biological half-life of clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by haemodialysis or peritoneal dialysis.

If an allergic adverse reaction occurs, therapy should be with the usual emergency treatments, including corticosteroids, adrenaline and antihistamines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lincosamides

ATC classification: 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.

Mechanism of 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 ≤ 0.5 resistant > 0.5

Streptococci ABCG and pneumoniae: sensitive ≤ 0.5 resistant > 0.5

Gram positive anaerobes: sensitive ≤ 4 resistant > 4

Gram negative anaerobes: ≤ 4 resistant > 4

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 pneumonia
Streptococcus pyogenes
Streptococcus viridans
Anaerobes
Bacteriodes fragilis group
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.

5.2 Pharmacokinetic properties

Absorption

After oral administration clindamycin is absorbed quickly and almost completely (>90%). The absorption is not affected by food. The peak plasma concentration is achieved within approximately 45 minutes after oral administration. The bioavailability is non-linear and decreases with increasing doses. Following a 600 mg dose the absolute bioavailability is 53±14%.

Distribution

Clindamycin is widely distributed in body fluids and tissues. It diffuses across the placenta but not the healthy blood-brain barrier. 68 – 93 % of clindamycin in the circulation is bound to plasma proteins. Clindamycin is distributed very highly intracellular due to the lipophilic properties. The intracellular concentrations are 10-50 times higher than the extracellular concentrations.

Biotransformation

Clindamycin undergoes metabolism, presumably in the liver, to the active N-demethyl and sulphoxide metabolites, and also some inactive metabolites and about 4% in the faeces: the remainder is excreted as inactive metabolites.

Elimination

Half-life is approximately two and a half hour in children and approximately 3 hours in adults. Clindamycin is excreted as biological active and biological inactive metabolites in faeces, urine and bile. Faecal excretion is predominant. About 10% of the drug is excreted in the urine as active drug and about 4% in the faeces; the remainder is excreted as inactive metabolites.

Characteristics in patients

Elderly:

The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate are not altered by increased age.

Patients with renal impairment:

In the presence of renal impairment, elimination half-life is prolonged; however, a dosage reduction is unnecessary in the event of mild to moderate impairment of renal function.

Patients with hepatic impairment:

In patients with moderate to severe hepatic impairment the half-life is prolonged, but when giving the dose every 8 hours, accumulation is rarely seen. Dose reduction is normally not necessary in patients with hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of repeat dose toxicity, reproductive toxicity or genotoxicity. Carcinogenicity studies have not been conducted.

In dogs, repeated high oral doses produced ulceration of the mucosa of the stomach and gall bladder.

5 PHARMACEUTICAL PARTICULARS

5.2 List of excipients

Maize Starch
Dibasic Calcium Phosphate
Purified Talc (Talcum)
Magnesium Stearate
Sodium Starch Glycolate
Colloidal Anhydrous Silica (Colloidal Silicon Dioxide)
E.H.G. CAPSULES SIZE 2 Red/White IH

5.3 Incompatibilities

Not applicable.

5.4 Shelf life

36 months from the date of manufacture

5.5 Special precautions for storage

Store below 30ºC. Protect from light.

5.6 Nature and contents of container <and special equipment for use, administration or implantation>

10 Capsules packed in one Alu-PVC Blister. Such 10 blister packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

Note: All Pack size may not be marketed.

5.7 Special precautions for disposal

No special requirements.

6 MANUFACTURER

Globela Pharma Pvt. Ltd.

Plot No. 357-358, GIDC, Road No. 3,

Sachin, Surat,Gujarat, India

Tel: 0261 6158000

E-mail: sales@globelapharma.com