Summary of Product Characteristics
CLINDAZEN 150
(Clindamycin Hydrochloride Capsules USP 150mg)

1. Name of the medicinal product:
CLINDAZEN 150 (Clindamycin Hydrochloride Capsules USP 150mg)

2. Qualitative and quantitative composition
Each hard gelatin capsule contains 150 mg Clindamycin Hydrochloride.

Excipients of known effect:
Each capsule contains 26.0 mg of lactose monohydrate (For the full list of excipients see section 6.1).

3. PHARMACEUTICAL FORM
Capsules
Light Blue Cap/ Light Blue Body, Size '2' Hard gelatin Capsules containing a 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 of administration
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. Clindamycin should be dosed based on total body weight regardless of obesity.
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. Capsules should always be swallowed whole and washed down with a full glass of water while in an upright position. Absorption of Clindamycin capsules is not appreciably modified by the presence of food.

4.3 Contraindications
Hypersensitivity to the active substance, lincomycin or to any of the excipients

4.4 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.
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.
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.

4.5 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.
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.

4.6 Fertility, 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 < 0.5 to 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

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

4.7 Effects on ability to drive and use machines

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

4.8 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.

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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*
Renal and urinary disorders			acute kidney injury
Skin and Subcutaneous Tissue Disorders			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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to National Regulatory Agents.

4.9 Overdose
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 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 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.
Mechanism of resistance
Resistance to clindamycin usually occurs via macrolide-lincosamide-streptogramin B (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: ≤ 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.

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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 hours 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.

Obese paediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years:

An analysis of pharmacokinetic data in obese paediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years demonstrated that clindamycin clearance and volume of distribution normalized by total body weight are comparable regardless of obesity

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.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Ingredients
1.	Lactose
2.	Maize Starch
3.	Magnesium Stearate
4.	Purified Talc
5.	Colloidal Anhydrous Silica
6.	Light Blue Cap/ Light Blue Body Size ‘2’ Hard Gelatin Capsules

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6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30^{O}C. Protect from light.

6.5 Nature and contents of container
1 ALU-ALU Blister of 10 Capsules, such 10 Blisters packed in Printed Carton with Insert.

6.6 Special precautions for disposal and other handling
No special requirements

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing Authorisation Holder:
ZAIN PHARMA LTD.
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice and Lovely House,
P.O. Box: 100167-00101, Nairobi, Kenya

8. Marketing Authorization Number: H2026/CTD12271/26748

9. Date of First <Registration> / Renewal of The <Registration>
Not Applicable

10. Date of Revision of the Text: Not Applicable