PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CEZLIN 150 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride USP equivalent to clindamycin 150 mg.

Contains sugar: 53.76 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Light blue opaque / Light green transparent size '1' hard gelatin capsule filled with white to off white powder imprinted with 'C' on light blue opaque cap & '39' on light green transparent body with black ink

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CEZLIN is indicated in serious infections caused by organism's susceptible (anaerobic bacteria) to its action. In vitro susceptibility studies should be performed. Infections due to sensitive organisms (serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci) which responds to an effective dose of this oral preparation include infections of the:

Upper respiratory tract including pharyngitis, tonsillitis, sinusitis, otitis media.

Lower respiratory including bronchitis, and pneumonia.

Skin and soft tissue including, abscesses, cellulitis, infected wounds, and dental infections (peri- apical abscesses and gingivitis).

Bones and joints including acute and chronic osteomyelitis.

Bacteraemia has responded to the usually recommended dosages.

4.2. Posology and method of administration

Posology

- **Adults:**

Mild to Moderately Severe Infection: 150 mg approximately every six hours.

Severe Infections: Up to 450 mg every six hours.

- **Paediatric population:**

Mild Infections: 8-12 mg/kg/day divided into 3 or 4 equal doses.

Moderately severe infections: 13-16 mg/kg/day divided into 3 or 4 equal doses.

Severe Infections: 17-25 mg/kg/day divided into 3 or 4 equal doses.

Do not give **CEZLIN** capsules to children weighing less than 10 kg.

Note: With ß-haemolytic streptococcal infections, treatment should continue for at least ten days to diminish the likelihood of subsequent severe complications such as rheumatic fever or glomerulonephritis.

Method of administration

CEZLIN capsules should be taken with a full glass of water to avoid the possibility of oesophageal irritation.

CEZLIN is not appreciably modified by the presence of food (see Section 5.2).

4.3. Contraindications

- Patients previously found to be hypersensitive to clindamycin, lincomycin or doxorubicin, or any of the excipients in **CEZLIN** listed in Section 6.1.

- Do not use in patients with diarrhoeal states or gastro-intestinal disease, particularly those with a history of colitis.
- Safety for use in pregnancy has not been established.
- Clindamycin has been reported to appear in breast milk. Do not use in lactation.

4.4. Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Severe hypersensitivity reactions, including severe skin reactions such as medicine reactions with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised 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 Sections 4.3 and 4.8).

CEZLIN should only be used in the treatment of serious infections. In considering the use of **CEZLIN**, 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 (see Section 4.8). (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 mucus. 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 **CEZLIN** 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 medicines, including clindamycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines 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 medicines.

Cross-resistance has been demonstrated between lincomycin hydrochloride and clindamycin hydrochloride. Antagonism with erythromycin has been demonstrated in vitro, therefore it is not recommended that the two medicines be given at the same time. Staphylococci resistant to erythromycin may also develop resistance to clindamycin. Since clindamycin does not diffuse adequately into cerebrospinal fluid, it should not be used in the treatment of meningitis.

Precautions: Caution should be used when prescribing **CEZLIN** to individuals with a history of gastro-intestinal disease, especially colitis.

Periodic liver and kidney function tests should be carried out during prolonged therapy.

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

Prolonged administration of **CEZLIN**, as with any anti-infective, may result in super-infection due to organisms resistant to clindamycin.

Care should be observed in the use of **CEZLIN** in atopic individuals.

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking medicines.

Therefore, it should be used with caution in patients receiving such medicines.

CEZLIN contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicines and other forms of interaction

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

Clindamycin may competitively inhibit the effects of macrolides, ketolides, streptogramins, linezolid, and chloramphenicol because they all bind to the same subunit of the ribosome. Antagonism between clindamycin and erythromycin has been shown in vitro (see Section 4.4).

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). 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 medicines metabolized by these CYP enzymes are unlikely.

4.6. Fertility, pregnancy and lactation

Pregnancy

Teratogenic effects

Clindamycin crosses the placenta in humans. **CEZLIN** should not be used during pregnancy as safety has not been established (see Section 4.3).

Breastfeeding

CEZLIN should not be used during breastfeeding (see Section 4.3).

Fertility

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.6 times the highest recommended adult human dose based on mg/m2) revealed no effects 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

Use of clindamycin had been associated with the development of diarrhoea in up to 20% of patients.

Skin rashes occur in 10 % of patients treated with clindamycin and may be more common in patients with HIV infection.

The table below lists the adverse reactions sorted by system organ class and frequency.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

a. Tabulated list of adverse reactions

System Organ Class	**Frequency Category**
Infections and infestations:	
Pseudomembranous colitis[#]	Frequent
Clostridium difficile colitis	Frequency unknown
Vaginal infection	
Blood and lymphatic disorders:	
Agranulocytosis	Frequency unknown
Neutropenia	
Thrombocytopenia	
Leukopenia	
Eosinophilia	
Immune system disorders:	

Anaphylactic shock	Frequency unknown
Anaphylactoid reaction	
Anaphylactic reaction	
Hypersensitivity	
Nervous system disorders:	
Dysgeusia	Frequency unknown
Gastrointestinal disorders:	
Diarrhoea	Frequent
Abdominal pain	
Vomiting	Less Frequent
Nausea	
Oesophageal ulcer	Frequency unknown
Oesophagitis	
Hepatobiliary Disorders	
Jaundice	Frequency unknown
Skin and subcutaneous tissues disorders:	
Rash maculo-papular	Less frequent
Urticaria	
Toxic epidermal necrolysis (TEN)	Frequency unknown
Stevens-Johnson syndrome (SJS)	
Medicine reaction with eosinophilia and systemic symptoms (DRESS)	
Acute generalised exanthematous pustulosis (AGEP)	
Angioedema	
Dermatitis exfoliative	
Dermatitis bullous	
Erythema multiforme	
Pruritus	

Rash morbilliform	
Investigations:	
Liver function test abnormal	Frequent

see Section 4.4, and Section 4.8.b Description of selected adverse reactions

b. Description of selected adverse reactions:

Treatment of antibiotic-associated colitis:

If persistent diarrhoea occurs during therapy, the medication should be discontinued. Significant diarrhoea occurring up to several weeks post-therapy should be managed as if antibiotic associated.

- Mild colitis: may respond to discontinuation of clindamycin alone.

- Moderate to severe colitis: discontinue clindamycin and treat with fluid, electrolyte and protein replacement.

- Severe colitis: In cases not responding to the above discontinue clindamycin and treat with appropriate fluid electrolyte and protein supplementation and with one of the following:

• vancomycin 125 to 500 mg orally, every 6 hours for 5 to 10 days

• metronidazole 250 to 500 mg orally, every 8 hours,

• bacitracin 25 000 units orally, 4 times a day or

• cholestyramine 4 grams orally, four times a day.

Relapses must be treated with a second course of the above medication.

Cholestyramine or colestipol resins bind to C. *difficile* toxin *in vitro*. If it is administered concurrently with vancomycin, it may be advisable to administer the medicines several hours apart, since the resins have been shown to bind to oral vancomycin (see Section 4.4).

Antiperistaltic antidiarrhoeals are not recommended since they may delay the removal of toxins from the colon, thereby prolonging and/or worsening the condition.

c. Other special population

Elderly Use

Reported clinical experience indicates that antibiotic-associated colitis and diarrhoea (due to *Clostridium difficile*) seen in association with most antibiotics occur more frequently in the elderly (> 60 years) and may be more severe. These patients should be carefully monitored for the development of diarrhoea. Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration (see section 5.2)**.**

d. 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. Talk to your Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form' found under SAHPRA's publications:

https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

The incidence of gastrointestinal side-effects is greater with higher doses. Haemodialysis and peritoneal dialysis are not effective means of removing the compound from the blood. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Lincocosamide antibiotics, ATC Code D10AF01

Mechanism of Action

Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is bacteriostatic.

Antimicrobial Activity

Clindamycin has been shown to be active against most of the isolates of the following microorganisms, both in vitro and in clinical infections.

Gram-positive bacteria

Staphylococcus aureus (methicillin susceptible strains), Streptococcus pneumoniae (penicillin susceptible strains), Streptococcus pyogenes.

Anaerobic bacteria

Clostridium perfringens, Fusobacterium necrophorum, Fusobacterium nucleatum, Peptostreptococcus anaerobius, Prevotella melaninogenica.

Resistant

Streptococcus faecalis, Escherichia coli, Shigella spp., Samlmonella spp.f

Proteus spp. and Pseudomonas spp.

5.2. Pharmacokinetic properties

Absorption

Clindamycin is rapidly absorbed after oral administration (peak blood levels occurred in 45 minutes). Bone and other body fluid levels are obtained rapidly.

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastro-intestinal tract; concentrations of 2 to 3 micrograms per ml occur within one hour after a 150 mg dose of clindamycin, with average

concentrations of about 0.7 micrograms per ml after 6 hours. After doses of 300 and 600 mg peak plasma concentrations of 4 and 8 micrograms per ml, respectively, have been reported. Absorption is not significantly diminished by food in the stomach but the rate of absorption may be reduced**.**

Distribution

Clindamycin is widely distributed in body fluids and tissues including bone, but it does not reach the CSF in significant concentrations. It diffuses across the placenta into the foetal circulation and has been reported to appear 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 patients with severe renal impairment.

Metabolism

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. Clindamycin undergoes metabolism, presumably in the liver, to the active Ndemethyl and sulphoxide metabolites, and also some inactive metabolites

Excretion

About 10% of a dose is excreted in the urine as active medicine 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.

Special Populations

Patients with Renal Impairment

Serum half-life of clindamycin is increased slightly in patients with markedly reduced renal function. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

Elderly Patients

The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin hydrochloride 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, therefore, should not be influenced by age alone.

After oral administration of clindamycin hydrochloride, the average elimination half-life is increased to approximately 4.0 hours (range 3.4–5.1 h) in the elderly compared to 3.2 hours (range 2.1 –4.2 h) in younger adults. The extent of absorption, however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate USNF

Corn Starch USNF

Talc USP

Magnesium Stearate USNF

Empty Hard Gelatin Capsule Shell (Light blue opaque / Light green transparent, Size ‘1’)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

Proposed Shelf-life is 24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

HDPE Container Pack (20's):

White opaque round 40 ml HDPE container with 33 mm neck finish closed with 33 mm white opaque polypropylene RS closure with wad having induction sealing liner. Each HDPE container also contains 1 gm of silica gel sachet.

HDPE Container Pack (100's):

White opaque round 120 ml HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene CR closure with wad having induction sealing liner. Each HDPE container also contains 1 gm of silica gel sachet.

These **CEZLIN** HDPE bottles shall be further packed in preprinted carton with a packaging leaflet.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd

Office 2, 100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

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South Africa

8. REGISTRATION NUMBER

52/20.1.1/0028

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12 October 2021

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