PROFESSIONAL INFORMATION LEAFLET: CLINDAMYCIN ACTOR

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

CLINDAMYCIN ACTOR 150 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin.

Contains sugar (lactose monohydrate): 214,08 mg per capsule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

Size 1 hard gelatine white-white capsules, with marking “CLIN 150”, filled with white crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLINDAMYCIN ACTOR is indicated in serious infections caused by organisms susceptible to its action. *In vitro* susceptibility studies should be performed. Infections due to sensitive organisms 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 infection: Up to 450 mg every six hours.

Method of administration:

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

Note:

With ß-haemolytic streptococcal infections, treatment should continue for at least 10 days to diminish the likelihood of subsequent severe complications such as rheumatic fever or glomerulonephritis.

4.3 Contraindications

- Hypersensitivity to clindamycin, lincomycin, doxorubicin, or to any of the excipients of CLINDAMYCIN ACTOR listed in Section 6.1.
- Patients with diarrhoeal states or gastro-intestinal disease, particularly those with a history of colitis.
- Safety for use in pregnancy has not been stablished (see Section 4.6).
- Clindamycin appears in breastmilk. Do not use in lactation (see Section 4.6).

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Clindamycin therapy (such as CLINDAMYCIN ACTOR) has been associated with pseudomembranous colitis which may be fatal. Toxins A and B produced by *Clostridium difficile* are regarded as the principal cause of *Clostridium difficile* associated diarrhoea (CDAD). Colitis 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 which, if allowed to progress, may produce peritonitis, shock and toxic megacolon. Diagnosis is made on basis of the clinical symptoms, and can be confirmed 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 the *Clostridium difficile*. CDAD and colitis have occurred during the administration or even two- or three-weeks following administration of clindamycin. The disease is likely to take a more severe course in older patients or in patients who are debilitated.

Treatment of antibiotic-associated colitis:

Should persistent diarrhoea occur 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:

- metronidazole 250 to 500 mg orally, every 8 hours;
- vancomycin 125 to 500 mg orally, every 6 hours for 5 to 10 days;
- 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 *Clostridium difficile* toxin *in vitro.* Should it be 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.

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

Complete cross-resistance exists between CLINDAMYCIN ACTOR and lincomycin or erythromycin (see Sections 4.5 and 5.1).

Clindamycin as contained in CLINDAMYCIN ACTOR does not diffuse adequately into cerebrospinal fluid, it should not be used in the treatment of meningitis.

CLINDAMYCIN ACTOR should be prescribed with caution in atopic patients.

During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. 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 therapy.

The use of CLINDAMYCIN ACTOR may result in overgrowth of non-susceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin as contained in CLINDAMYCIN ACTOR 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 (see Section 4.5).

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 generalised exanthematous pustulosis (AGEP) have been reported in patients receiving clindamycin as contained in CLINDMAYCIN ACTOR. If a hypersensitivity or severe skin reaction occurs, CLINDAMYCIN ACTOR should be discontinued and appropriate therapy should be initiated (see Sections 4.3 and 4.8).
CLINDAMYCIN ACTOR contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take CLINDAMYCIN ACTOR.

4.5 Interaction with other medicines and other forms of interaction
CLINDAMYCIN ACTOR may reduce the contraceptive effect of oestrogen.

Cross-resistance has been demonstrated between lincomycin hydrochloride and clindamycin hydrochloride (see Sections 4.4 and 5.1).

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 with macrolides such as erythromycin and streptomycin has been demonstrated *in vitro,* therefore it is not recommended that the two medicines be given at the same time.

Staphylococci which are resistant to erythromycin may also develop resistance to clindamycin.

Clindamycin as in CLINCAMYCIN ACTOR has neuromuscular blocking activity in high doses and may enhance the effect of other medicines with this action, with a potential danger of respiratory depression.

CLINDAMYCIN ACTOR antagonises the effects of acetylcholinesterases such as neostigmine and pyridostigmine.

Oral typhoid vaccine is inactivated by concomitant administration of antibacterials. Therefore, CLINDAMYCIN ACTOR should be avoided for 3 days before and after oral typhoid vaccination.
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.

Clindamycin is metabolised 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 as contained in CLINDAMYCIN ACTOR does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6 and only moderately inhibits CYP3A4. Therefore, clinically important interactions between clindamycin and co-administered medicines metabolised by these CYP enzymes are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of CLINDAMYCIN ACTOR for use in pregnancy has not been established (see Section 4.3).

Breastfeeding:

Clindamycin as contained in CLINDAMYCIN ACTOR is excreted in breastmilk and may cause diarrhoea or fungal infections in the infants. Therefore, it is contraindicated in mothers breastfeeding their infants (see Section 4.3).

4.7 Effects on ability to drive and use machines

CLINDAMYCIN ACTOR is not known to have an effect on cognitive ability. However, patients should be advised to exercise caution until they know how CLINDAMYCIN ACTOR affects them.

4.8 Undesirable effects

Adverse reactions:

The following side effects have been reported with clindamycin such as CLINDAMYCIN ACTOR.

Table 1: Tabulated summary of adverse reactions

System organ class	**Side effects**
Infections and infestations *Frequent:* *Frequency unknown:*	 Pseudomembranous colitis. Vaginal infection, *Clostridium difficile* infection.
Blood and lymphatic system disorders *Frequency unknown:*	 Neutropenia (leucopenia), eosinophilia, agranulocytosis, thrombocytopenia.
Immune system disorders *Frequency unknown:*	 Anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity, angioedema.
Nervous system disorders *Frequency unknown:*	 Dysgeusia.
Gastrointestinal disorders *Frequent:* *Less frequent:*	 Abdominal discomfort/pain, diarrhoea, oesophagitis, nausea, vomiting. Oesophageal ulcer.
Hepato-biliary disorders *Frequency unknown:*	 Jaundice.
Skin and subcutaneous tissue disorders *Frequent:* *Less frequent:* *Frequency unknown:*	 Rash morbilliform. Rash maculopapular, urticaria. Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative, dermatitis bullous, erythema multiforme, pruritus.
Musculoskeletal and connective tissue disorders *Frequency unknown:*	 Polyarthritis.
Investigations *Frequent:*	 Abnormal liver function test

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of CLINDAMYCIN ACTOR is important. It allows continued monitoring of the benefit/risk balance of CLINDAMYCIN ACTOR. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Actor Pharma (Pty) Ltd via email: pharmacovigilance@actorpharma.co.za or telephonically on 011 312 3812.

4.9 Overdose

See section 4.8

The incidence of gastro-intestinal side effects is greater with higher doses of CLINDAMYCIN ACTOR. Peritoneal dialysis and haemodialysis are not effective means of removing the compound from the blood. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A 20.1.1 Broad and medium spectrum antibiotics

Clindamycin hydrochloride binds exclusively to the 50 S subunit of bacterial ribosomes and suppresses protein synthesis. It has antibacterial activity against gram-positive organisms and a lower order of activity against gram-negative organisms. *In vitro* activity does not necessarily imply *in vivo* efficacy. Clindamycin hydrochloride is not active against most strains of *Streptococcus faecalis, Escherichia coli, Shigella spp., Salmonella spp., Proteus spp.,* and *Pseudomonas spp.*

Resistant organisms:

Most Gram-negative aerobic bacteria, including the enterobacteriaceae, *Pseudomonas spp.,* and *Acinetobacter spp.,* are intrinsically resistant to clindamycin.

Neisseria gonorrhoeae, N. meningitides, Haemophilus influenza, Mycoplasma spp. and *Mycobacterium tuberculosis* are resistant to clindamycin.

Fungi, yeast and viruses are also resistant to clindamycin.

Complete cross-resistance exists between clindamycin and lincomycin (see Sections 4.4 and 4.5).

Gram-negative anaerobe, *Fusobacterium varium*, is usually resistant to clindamycin.

5.2 Pharmacokinetic properties

Absorption:

Clindamycin hydrochloride is well absorbed after oral administration (peak blood levels occurred in 45 minutes). Bone as well as other body fluid levels are obtained rapidly. Absorption is almost complete at

90 %. Blood levels exceed the minimum inhibitory concentration (MIC) for most indicative organisms for at least six hours following the administration of the usually recommended doses.

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. *In vitro* studies in human liver and intestinal microsomes indicated that clindamycin is predominantly oxidised 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.

Metabolism:

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

Excretion:

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

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Talc
Vegetable magnesium stearate

Capsule shell
Titanium dioxide (E171)
Gelatine
Printing Ink
Shellac
Iron oxide black (E172)
Propylene glycol (E1520)
Ammonium hydroxide (E527)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C in a cool, dry place.

Store in the original packaging in order to protect from light and moisture.

Store all medicines out of reach of children.

6.5 Nature and contents of container

Aluminium-PVC blister strips containing 20, 24 or 100 capsules.

Not all pack sizes may be marketed.

The Aluminium-PVC blisters are contained in an outer cardboard carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Actor Pharma (Pty) Ltd[1]
Royal Palm Business Estate
Unit 7, 646 Washington Street
Halfway House, Midrand, 1685
Gauteng, South Africa

8. REGISTRATION NUMBER(S)

48/20.1.1/0806

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 March 2021

10. DATE OF REVISION OF THE TEXT

Not applicable

[1] Company Registration Number.: 2008/008787/07