SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Clindamycin Equity, 150 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:

Contains sugar (lactose monohydrate 98,13 mg per capsule).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Hard capsule no. 1, pink opaque cap and maroon opaque body colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clindamycin Equity 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 infections: Up to 450 mg every six hours.

Special populations

Elderly patients

The half-life, volume of distribution, clearance and extent of absorption after administration of clindamycin 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.

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.

Clindamycin Equity capsules should only be used for children who are able to swallow capsules.

Do not give Clindamycin Equity capsules to children weighing less than 10 kg. The use of whole capsules may not be suitable to provide the exact mg/kg doses required for the treatment of children.

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

For oral use.

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

4.3 Contraindications

- Patients previously found to be hypersensitive to clindamycin, lincomycin or doxorubicin or to any of the excipients listed in section 6.1.
- Do not use in patients with diarrhoeal states or gastrointestinal 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 should adhere to the principles of antibiotic stewardship.

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 generalised exanthematous pustulosis (AGEP) have been reported in patients receiving clindamycin therapy. If a hypersensitivity or severe skin reaction occurs, Clindamycin Equity should be discontinued and appropriate therapy should be initiated (see sections 4.3 and 4.8).

Clindamycin Equity should only be used in the treatment of serious infections. In considering the use of the product, the medical 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 following the administration of

clindamycin.

Clindamycin Equity-associated colitis may end fatally. Toxins produced by *Clostridium difficile* are regarded as the principal cause of antibiotic-associated colitis. Colitis has a clinical spectrum from mild, watery diarrhoea to severe, persistent diarrhoea, leucocytosis, fever and 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 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 the *C. difficile*. Antibiotic-associated colitis has occurred during the administration or even two to three weeks following administration of Clindamycin Equity. The disease is likely to take a more severe course in older patients or in patients who are debilitated. For treatment of antibiotic-associated colitis see section below.

Treatment of antibiotic-associated colitis

If persistent diarrhoea occurs during therapy, Clindamycin Equity 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 Equity alone.
- *Moderate colitis:* Discontinue Clindamycin Equity and treat with fluid, electrolyte and protein replacement.
- *Severe colitis:* In cases not responding to the above, discontinue Clindamycin Equity 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
    - cholestyramine 4 grams orally, four times a day

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

Cholestyramine and colestipol resins bind to *C. difficile* toxin *in vitro*. When administered concurrently with vancomycin, it is advisable to administer the medicines several hours apart since the resins have been shown to bind to oral vancomycin.

Anti-peristaltic anti-diarrhoeals are not recommended since they may delay the removal of toxins from the colon, thereby prolonging and/or worsening the condition.

Cross-resistance has been demonstrated between lincomycin hydrochloride and Clindamycin Equity.

Since Clindamycin Equity does not diffuse adequately into cerebrospinal fluid, it should not be used in the treatment of meningitis.

Clindamycin Equity should be prescribed with caution in atopic individuals or in patients with a history of gastrointestinal disease, particularly colitis.

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

Lactose intolerance

Clindamycin Equity contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Clindamycin Equity.

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.

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 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 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Clindamycin as contained in Clindamycin Equity crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30 % of maternal blood concentrations.

Safety for use in pregnancy has not been established.

Breastfeeding

Clindamycin Equity has been reported to appear in human breast milk in ranges from < 0,5 to 3,8 µg/mL. Because of the potential for serious adverse reactions in nursing infants, Clindamycin Equity should not be taken by nursing mothers (see section 4.3).

Fertility

Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability. There is no clinical data on human fertility.

4.7 Effects on ability to drive and use machines

The effect of Clindamycin Equity on the ability to drive or operate machinery has not been systemically evaluated.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effect**
Blood and lymphatic system disorders	Frequent	Eosinophilia
Nervous system disorders	Less frequent	Dysgeusia
Gastrointestinal disorders	Frequent	Diarrhoea, abdominal pain
	Less frequent	Vomiting, nausea
Skin and subcutaneous tissue disorders	Frequent	Maculopapular rash
	Less frequent	Urticaria, erythema multiforme, pruritus
Investigations	Frequent	Abnormalities in liver function test (elevation of alkaline phosphatases and serum transaminases)

Post-marketing experience

Adverse reactions identified from post-marketing experience include the following:

System Organ Class	**Side effect**
Infections and infestations	Pseudomembranous colitis, *clostridium difficile* colitis, vaginal infection
Blood and lymphatic system disorders	Agranulocytosis, neutropenia, leukopenia, thrombocytopenia
Immune system disorders	Anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity
Gastrointestinal disorders	Oesophageal ulcer, oesophagitis
Hepato-biliary disorders	Jaundice
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), angioedema, exfoliative dermatitis, bullous dermatitis, morbilliform rash

Paediatric population

Adverse reactions in children are not expected to be different than in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The incidence of gastro-intestinal side effects is greater with higher doses.

Haemodialysis and peritoneal dialysis are not effective means of removing clindamycin 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: Antibacterials for systemic use, 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 protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains. *In vitro* activity does not necessarily imply *in vivo* efficacy.

Resistance

Resistance to clindamycin usually occurs via macrolide-lincosamide-streptogramin B (MLSB) type of resistance, which may be constitutive or inducible.

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).

5.2 Pharmacokinetic properties

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.

Clindamycin is widely distributed in body fluids and tissues including bone, but it does not reach the csf (cerebrospinal fluid) 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 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose Monohydrate

Maize starch

Magnesium Stearate

Talc

Capsule shell

FD&C Blue 1 (E133)

FD&C Blue 3 (E127)

Gelatin

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the capsules in the blister in the outer carton until required for use.

6.5 Nature and contents of container

Clindamycin Equity capsules are packed in blisters containing 10 capsules each. The blisters are packed in quantities of 5 in an outer box.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

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Route 21 Corporate Park

Nellmapius Drive

Irene 0157

Pretoria

South Africa

8. REGISTRATION NUMBER(S)

56/20.1.1/0105

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 May 2023

10. DATE OF REVISION OF THE TEXT