SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DALACIN® C 150 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (lactose monohydrate).

Excipients with known effect

Each capsule contains approximately 209,5 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

Hard gelatin capsule (number 1 size) with white cap and white body marked with “Clin 150” and “Pfizer” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DALACIN C is indicated in serious infections caused by susceptible Gram-positive organisms, staphylococci (both penicillinase- and non-penicillinase-producing), streptococci (except *Streptococcus faecalis*) and pneumococci. It is also indicated for serious infections caused by susceptible anaerobic

pathogens. *In vitro* susceptibility studies should be performed. Infections due to sensitive organisms which respond to an effective dose of this oral preparation include infections of the:

- Upper respiratory tract including pharyngitis, tonsillitis, sinusitis, otitis media.
- Lower respiratory tract including bronchitis and pneumonia.
- Skin and soft tissue including abscesses, cellulitis, infected wounds, and dental infections (periapical 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 infections

150 mg approximately every six hours.

Severe infections

Up to 450 mg every six hours.

Elderly patients

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

DALACIN C capsules should only be used for children who are able to swallow capsules. Do not give DALACIN C 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.

Patients with renal and hepatic impairment

DALACIN C dosage modification is not necessary in patients with renal or hepatic insufficiency (see section 5.2).

During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Patients with severe renal or severe hepatic disease or with severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high dose therapy.

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.

The capsules must be swallowed whole and not chewed, crushed or opened because of unpleasant taste and possible buccal and oesophageal irritation.

Absorption of DALACIN C is not appreciably modified by the presence of food.

4.3 Contraindications

- Patients with known hypersensitivity to clindamycin, lincomycin or doxorubicin or to any of the excipients of DALACIN C (listed in section 6.1).
- 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.

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 DALACIN C therapy. If a hypersensitivity or severe skin reaction occurs, DALACIN C should be discontinued and appropriate therapy should be initiated (see sections 4.3 and 4.8).

DALACIN C should only be used in the treatment of serious infections. In considering the use of the product, the health care provider should bear in mind the type of infection and the potential hazard of diarrhoea which may develop, since cases of colitis have been reported following the administration of DALACIN C.

DALACIN C-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 DALACIN C. 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, DALACIN C 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 DALACIN C alone.
- *Moderate colitis:* Discontinue DALACIN C and treat with fluid, electrolyte and protein replacement.
- *Severe colitis:* In cases not responding to the above, discontinue DALACIN C 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 DALACIN C.

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

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

Acute kidney injury, including acute renal failure, has been reported infrequently. In patients suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic medicines, monitoring of renal function should be considered (see section 4.8).

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

DALACIN C 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

DALACIN C 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.

Co-administration of DALACIN C with inhibitors of CYP3A4 and CYP3A5

DALACIN C 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 DALACIN C clearance and inducers of these isoenzymes may increase DALACIN C clearance. In the presence of strong CYP3A4 inducers such as rifampicin, monitor for loss of effectiveness.

In vitro studies indicate that DALACIN C does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6 and only moderately inhibits CYP3A4. Therefore, clinically important interactions between DALACIN C and co-administered medicines metabolised by these CYP enzymes are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

DALACIN C is contraindicated in pregnancy as safety has not been demonstrated (see section 4.3).

DALACIN C crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30 % of maternal blood concentrations.

Breastfeeding

DALACIN C 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, DALACIN C should not be taken by breastfeeding mothers (see section 4.3).

Fertility

Fertility studies in rats treated orally with DALACIN C revealed no effects on fertility or mating ability.

4.7 Effects on ability to drive and use machines

The effect of DALACIN C on the ability to drive or operate machinery has not been systematically evaluated.

4.8 Undesirable effects

Tabulated summary of adverse reactions

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

System organ class	**Frequency**	**Side effect**
Blood and lymphatic system disorders	Common	Eosinophilia
Nervous system disorders	Uncommon	Dysgeusia
Gastrointestinal disorders	Common	Diarrhoea, abdominal pain
	Uncommon	Vomiting, nausea
Skin and subcutaneous tissue disorders	Common	Maculopapular rash
	Uncommon	Urticaria
	Rare	Erythema multiforme, pruritus

Investigations	Common	Abnormalities in liver function test (elevations 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
Renal and urinary disorders	Acute kidney injury (see section 4.4)

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. Health care 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 gastrointestinal side effects is greater with higher doses. Haemodialysis and peritoneal dialysis are not effective means of removing DALACIN C from the blood. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

Clindamycin hydrochloride is a lincosamide antibiotic that binds exclusively to the 50 S subunit of bacterial ribosomes and suppresses protein synthesis. The action of clindamycin is predominantly bacteriostatic. Clindamycin hydrochloride 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.*

Resistance

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

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 medicine in at least some types of infections is questionable.

Up to 50 % of methicillin-susceptible *Staphylococcus aureus* have been reported to be resistant to clindamycin in some areas. More than 90 % of methicillin-resistant *Staphylococcus 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

Clindamycin hydrochloride is rapidly absorbed after oral administration (peak blood levels occurred in 45 minutes). Bone and other body fluid levels are obtained rapidly. Absorption is almost complete (90 %); 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. Blood levels exceed the minimum inhibitory concentration (MIC) for most indicated organisms for at least six hours following administration of the usually recommended doses.

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 biological half-life is 2,4 hours.

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. Clindamycin is not effectively removed from the blood by dialysis.

Renal impairment

The pharmacokinetics of clindamycin were compared between subjects with normal renal function (n=4) and those with chronic renal failure during dialysis (n=4) and after dialysis (n=5). The half-life of clindamycin was 2,15 hours in the subjects with normal renal function, 1,85 hours during dialysis, and 1,58 hours after dialysis. Clindamycin is excreted normally in chronic renal failure and the clindamycin blood levels were not affected by haemodialysis. In another study, after a single intramuscular injection of 300 mg of clindamycin to 6 normal subjects and 6 patients during and after haemodialysis, clindamycin peak levels tended to be higher while the half-lives were shorter in the dialysis patients than in the normal subjects. Clindamycin concentrations at 6 hours post dose in normal subjects was 2,33 µg/mL, during haemodialysis 3,05 µg/mL and after haemodialysis 3,03 µg/mL, with the respective half-lives of 3,49, 2,15 and 2,83 hours. In five anuric patients, clindamycin serum concentrations at 12 hours post dose were 0,71 µg/mL during haemodialysis and 0,73 µg/mL during a non-dialysis interval, and the respective half-lives (hours) of 3,14 and 3,36. Clindamycin pharmacokinetics are not affected by renal impairment and haemodialysis, therefore, dosage modification is not necessary in patients with renal impairment.

Hepatic impairment

The clearances for clindamycin following a single 600 mg intravenous (IV) dose in healthy adults (n=4), in patients with virus or medicine induced hepatitis (n=5) and in patients with chronic hepatocellular liver disease (n=8) were (mL/min/kg), respectively, 4,11±0,54, 2,64±1,47 and 2,19±1,18, and the respective elimination half-lives (hours) were 2,00 ±0,75, 4,41±1,67 and 4,96±1,89. Clindamycin exposure was approximately 2-fold higher; clearance was approximately 2-fold slower and elimination half-life was 2-fold longer in hepatic impairment patients compared to healthy adult subjects. This implies that pharmacokinetic parameters of clindamycin were comparable between those of patients with virus or medicine induced hepatitis and in patients with chronic hepatocellular liver disease. In another study, clindamycin 300 mg IV was given every 12 hours for 2 days in patients with acute hepatitis (n=7), chronic hepatitis (n=6), liver cirrhosis (n=9) and healthy adults (n=8). Clindamycin serum levels between the controls and acute and chronic hepatitis patients were not statistically significantly different. Whereas,

clindamycin serum levels in liver cirrhosis patients were significantly higher than the control patients after both first and third dose, clindamycin elimination half-life was 1,8, 2,6, 2,1 and 2,5 hours in control, acute hepatitis, chronic hepatitis and liver cirrhosis patients, respectively. Although clindamycin half-life is prolonged in patients with moderate or severe liver disease, medicine accumulation is unlikely to occur when administered on an every-8-hour schedule. Thus, dosage modification is not necessary in patients with hepatic insufficiency.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Lactose monohydrate

Magnesium stearate

Starch maize

Talc

Capsule shell

Gelatin

Titanium dioxide

Printing ink

Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

DALACIN C 150 mg capsules are packed in glass bottles and blisters containing 20 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

C/20.1.1/1

9. DATE OF FIRST AUTHORISATION

07 August 1970

10. DATE OF REVISION OF THE TEXT

17 January 2022

BOTSWANA: S2

Reg. No.: B9311965

NAMIBIA: NS2

Reg. No.: 90/20.1.1/001302

ZAMBIA: POM

Reg. No.: 120/023

Manufacturer: Fareva Amboise, Pocé-sur-Cisse, France