SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Clindamycin phosphate 150mg/ml solution for injection
Dalacin C Phosphate

2. Qualitative and quantitative composition

Each ml of solution contains clindamycin phosphate equivalent to 150mg clindamycin.
Excipients with known effect
Each ml of solution contains 9mgof benzyl alcohol. See section 4.4.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection
Clear, colourless, sterile solution for intramuscular or intravenous use.

4. Clinical particulars

4.1 Therapeutic indications

Antibacterial. 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 in serious infections caused by susceptible anaerobic pathogens such as *Bacteroides* spp, *Fusobacterium* spp, *Propionibacterium* spp, *Peptostreptococcus* spp. and microaerophilic streptococci.
Clindamycin does not penetrate the blood/brain barrier in therapeutically effective quantities.

4.2 Posology and method of administration

Parenteral (IM or IV administration) - 'see Method of administration' below.
Posology
Adults
Serious infections: 600mg- 1.2 g/day in two, three or four equal doses.
More severe infections: l.2-2.7 g/day in two, three or four equal doses.
Single IM injections of greater than 600mgare not recommended nor is administration of more than 1.2 g in a single one-hour infusion.
For more serious infections, these doses may have to be increased. In life-threatening situations, doses as high as 4.8 g daily have been given intravenously to adults.
Alternatively, the drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion.
Treatment for infections caused by beta-haemolytic streptococci should be continued for at least 10 days to guard against subsequent rheumatic fever or glomerulonephritis.
Paediatric population (over 1 month in age)
Serious infections: 15-25mg/kg/day in three or four equal doses.
Clindamycin should be dosed based on total body weight regardless of obesity.

More severe infections: 25-40mg/kg/day in three or four equal doses. In severe infections it is recommended that children be given no less than 300mg/day regardless of body weight.

Elderly patients

The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate 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 should not be influenced, therefore, by age alone. See *Precautions* for other factors which should be taken into consideration.

Method of administration

Parental (IM or IV administration).

Dalacin C Phosphate should be used undiluted for IM administration.

Dalacin C Phosphate **must** be diluted prior to IV administration and should be infused over at least 10-60 minutes.

Dilution for IV use and IV infusion rates

The concentration of clindamycin in diluent for infusion should not exceed 18mgper ml and INFUSION RATES SHOULD NOT EXCEED 30mgPER MINUTE. The usual infusion rates are as follows:

Dose	Diluent	Time
300mg	50ml	10min
600mg	50ml	20min
900mg	50-100ml	30min
1200mg	100ml	40min

4.3 Contraindications

Dalacin C Phosphate is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin, any component of the formulation, or to any excipients listed in section 6.1.

Clindamycin phosphate solution for injection must not be given to premature babies or neonates because of the benzyl alcohol content (see section 4.6).

4.4 Special warnings and precautions for use

Warnings

Dalacin C Phosphate contains benzyl alcohol (see section 2). The preservative benzyl alcohol may cause hypersensitivity reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events, and death in paediatric patients including neonates ("gasping syndrome"). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol containing formulations should only be used in neonates if it is necessary and if there are no alternatives possible. Premature and low-birth weight neonates may be more likely to develop toxicity. Benzyl alcohol containing formulations should not be used for more than 1 week in children under 3 years of age unless necessary. It is important to consider the total quantity of benzyl alcohol received from all sources, and high volumes should be used with caution and only if necessary, especially in patients with liver or kidney impairment, as well as in pregnant or breast-feeding women, because of the risk of accumulation and toxicity (metabolic acidosis).

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 (see sections 4.3 and 4.8).

Dalacin C Phosphate 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.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile.* This has been reported with use of nearly all antibacterial agents, including clindamycin. *Clostridium difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhoea (CDAD) and is a primary cause of 'antibiotic-associated colitis'. 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. 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 presence of the disease may be further confirmed by culture of the stool for *C. difficile* on selective media and assay of the stool specimen for the toxin(s) of *C. difficile*.

It is important to consider the diagnosis of CDAD in patients who present with diarrhoea subsequent to the administration of antibacterial agents. This may progress to colitis, including pseudomembranous colitis (see section 4.8), which may range from mild to fatal colitis. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including clindamycin, should be discontinued and adequate therapeutic measures should be initiated immediately. When 125mgto 500mgof 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. Drugs inhibiting peristalsis are contraindicated in this situation.

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.

<u>Precautions</u>

Caution should be used when prescribing Dalacin C Phosphate 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.

If therapy is prolonged, liver and kidney function tests should be performed. Such monitoring is also recommended in neonates and infants. Safety and appropriate dosage in infants less than one month old have not been established.

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 (see section 4.8).
The use of clindamycin phosphate may result in overgrowth of non-susceptible organisms, particularly yeasts.
Prolonged administration of Dalacin C Phosphate, as with any anti-infective, may result in super-infection due to organisms resistant to clindamycin.
Care should be observed in the use of Dalacin C Phosphate in atopic individuals.
Clindamycin phosphate should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes as directed in section 4.2.
Excipient information
Dalacin C Phosphate contains less than 1 mmol sodium (23mg) in each ampoule (2 ml or 4 ml), that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction
Clindamycin administered by injection has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution, in patients receiving such agents.
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
Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.
Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal blood concentrations.
Dalacin C Phosphate contains benzyl alcohol as a preservative. Benzyl alcohol can cross the placenta (see section 4.4).
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.

Breast-feeding

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.

Dalacin C Phosphate contains benzyl alcohol as a preservative (see section 4.4).

Fertility

Fertility studies in rats treated orally with clindamycin 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

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.

System Organ Class	**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**	**Not Known (cannot be estimated from available data)**
Infections and Infestations	pseudomembranous 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			
Cardiac Disorders		cardiorespiratory arrest †§,			
Vascular Disorders	thrombophlebitis†	hypotension†§			
Gastrointestinal Disorders		diarrhoea, nausea,			abdominal pain, vomiting, oesophageal ulcers, oesophagitis
Hepatobiliary Disorders					jaundice*
Skin and Subcutaneous Tissue Disorders	rash maculopapular	urticaria erythema multiforme, pruritus			toxic epidermal necrolysis (TEN)*, Stevens-Johnson syndrome (SJS)*, drug reaction with eosinophilia and systemic symptom (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis exfoliative*, dermatitis bullous*, rash morbilliform*,
Renal and urinary disorders					acute kidney injury#
General Disorders and Administrative Conditions		pain†, injection site abscess†			injection site irritation†*
Investigations	liver function test abnormal				

* ADR identified post-marketing.
† ADRs apply only to injectable formulations.
# See section 4.4.
§ Rare instances have been reported following too rapid intravenous administration (see section 4.2).
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 via the Medicines Control Authority of Zimbabwe website: www.mcaz.co.zw.

4.9 Overdose

In cases of overdosage no specific treatment is indicated.
The serum biological half-life of lincomycin is 2.4 hours. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.
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

Pharmacological Classification: 7.2.5 Other Antibacterial

Mode 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. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin.

Resistance

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

Breakpoints

The minimum inhibitory concentrations (MIC) breakpoints are as follows:
EUCAST
Staphylococci: sensitive ≤ 0.25 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

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).

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.

Species
Susceptible
Gram-positive aerobes

*Staphylococcus aureus**
Staphylococcus epidermidis
Streptococcus pneumonia
Streptococcus pyogenes
Viridans streptococci
Anaerobes
Bacteriodes fragilis group
Prevotella formerly known as 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.
Most gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin. Clindamycin demonstrates cross-resistance with lincomycin. When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly developed resistance to clindamycin. The mechanisms for resistance are the same as for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein and in a few staphylococcal isolates enzymic inactivation by a plasmid-mediated adenyltransferase.

5.2 Pharmacokinetic properties
General characteristics of active substance
Following parenteral administration, the biologically inactive clindamycin phosphate is hydrolysed to clindamycin. When the equivalent of 300mgof clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 microgram/ml is achieved within three hours; 600mggives a peak concentration of 9 microgram/ml . In children, peak concentration may be reached within one hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms per ml respectively are achieved by the end of infusion.
Clindamycin is widely distributed in body fluids and tissues including bone, but it does not reach the cerebrospinal fluid in significant concentrations. It diffuses across the placenta into the foetal circulation and appears 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, to the active *N*-demethyl and sulfoxide metabolites and also some inactive metabolites. About 10% of the drug is excreted in the urine as active drug 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.
Characteristics in patients
No special characteristics. See section 4.4 for further information.
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
Impairment of fertility
Fertility studies in rats treated orally with up to 300mg/kg/day (2-fold the human exposure based onmg/m^2) revealed no effects on fertility or mating ability.
Pregnancy
In oral embryo-foetal development studies in rats and subcutaneous embryo-foetal development studies in rats and rabbits, embryo-foetal toxicity was observed at doses that produced maternal toxicity. In rats, maternal death occurred with an exposure ratio of approximately 1 relative to patient exposure. In rabbits, maternal toxicity, including abortions, occurred at exposure ratio of approximately 0.1. Embryo-foetal toxicity, including post-implantation loss and decreased viability, occurred in rabbits at an exposure ratio of 0.2.
Carcinogenesis
Long-term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential.
Mutagenesis
Genotoxicity tests performed included a rat micronucleus test and an Ames test.
Both tests were negative.

6. Pharmaceutical particulars

6.1 List of excipients
Benzyl alcohol (E1519)
Disodium edetate
Sterilised water for injections

6.2 Incompatibilities
Solutions of clindamycin salts have a low pH and incompatibilities may reasonably be expected with alkaline preparations or drugs unstable at low pH. Incompatibility has been reported with: ampicillin sodium, aminophylline, barbiturates, calcium gluconate, ceftriaxone sodium, ciprofloxacin, diphenylhydantoin, idarubicin hydrochloride, magnesium sulfate, phenytoin sodium and ranitidine hydrochloride.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container
Type 1 flint glass ampoule containing 2 ml or 4 ml sterile, aqueous solution, packed in cardboard carton, together with a leaflet.

6.6 Special precautions for disposal and other handling
Dalacin C Phosphate has been shown to be physically and chemically compatible for at least 24 hours in dextrose 5% water and sodium chloride injection solutions containing the following antibiotics in usually administered concentrations: Amikacin sulfate, aztreonam, cefamandole nafate, cephazolin sodium, cefotaxime sodium, cefoxitin sodium, ceftazidime sodium, ceftizoxime sodium, gentamicin sulfate, netilmicin sulfate, piperacillin and tobramycin.
The compatibility and duration of stability of drug admixtures will vary depending upon concentration and other conditions.

7. Applicant
Pfizer Laboratories (Pty) Ltd
85 Bute Lane
2196 Sandton
South Africa

8. Manufacturer
Pharmacia Nv/S.A
Rijksweg 12
B-2870 Puurs
Belgium

9. Registration Details
Zimbabwe registration number: 3/20.1.1/

Zimbabwe Category for Distribution: Prescription Preparations (P.P.)

10. Date of revision of the text
April 2022