SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

WARNING

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin phosphate and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.

Because clindamycin phosphate therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the **INDICATIONS** section. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. *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 agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficil*e, and surgical evaluation should be instituted as clinically indicated.

1. TRADE NAME OF THE MEDICINAL PRODUCT

Dalacin C 150 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains clindamycin phosphate equivalent to 150 mg clindamycin.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

Clear, colourless, sterile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dalacin C (clindamycin phosphate) is indicated for the treatment of infections caused by susceptible anaerobic bacteria.

Clindamycin does not penetrate the blood/brain barrier in therapeutically effective quantities.

4.2 Posology and method of administration

Parenteral (IM or IV administration). Dalacin C (clindamycin phosphate) must be diluted prior to IV administration and should be infused over at least 10-60 minutes.

Adults:

Serious infections: 600 mg-1.2 g/day in two, three or four equal doses.

More severe infections: 1.2-2.7 g/day in two, three or four equal doses.

Single IM injections of greater than 600 mg are 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.

Children (over 1 month of age):

Serious infections: 15-25 mg/kg/day in three or four equal doses.

More severe infections: 25-40 mg/kg/day in three or four equal doses.

In severe infections it is recommended that children be given no less than 300 mg/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.

Dosage in renal/hepatic impairment:

Clindamycin dosage modification is not necessary in patients with renal or hepatic insufficiency.

The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL and INFUSION RATES SHOULD NOT EXCEED 30 MG PER MINUTE. The usual infusion rates are as follows:

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

4.3 Contra-indications

Dalacin C 150 mg/ml (clindamycin phosphate) is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin or to any component of the formulation.

4.4 Special warnings and special precautions for use

Warnings

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping syndrome" in premature infants.

Dalacin C 150 mg/ml (clindamycin 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.

Since clindamycin does not diffuse adequately into cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

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. (Where the patient is receiving colestyramine 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 the product 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 *C. difficile* on selective media and assay of the stool specimen for the toxin(s) of *C. difficile*.

After the primary diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents 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 agents.

Precautions

Caution should be used when prescribing Dalacin C 150 mg/ml (clindamycin phosphate) to individuals with a history of gastro-intestinal disease, especially colitis.

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

Prolonged administration of Dalacin C 150 mg/ml (clindamycin phosphate), as with any anti-infective, may result in super-infection due to organisms resistant to clindamycin, particularly yeasts.

Care should be observed in the use of Dalacin C 150 mg/ml (clindamycin phosphate) in atopic individuals.

4.5 Interaction with other medicaments and other forms of interaction

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

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance, the two drugs should not be administered concurrently.

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.

4.6 Pregnancy and lactation

Pregnancy: Teratogenic effects Pregnancy category B

Benzyl alcohol can cross the placenta. See section 4.4 **"Special warnings and special precautions for use"**.

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.

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.

Use in nursing mothers

Clindamycin has been reported to appear in human breast milk in ranges from 0.7 to 3.8 μg/mL at dosages of 150 mg orally to 600 mg intravenously. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

All undesirable effects listed in the label are presented by MedDRA SOC. Within each frequency category, the undesirable effects are presented in the order of frequency* and then of clinical importance.

Adverse Reactions Table

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	Frequency not known (cannot be estimated from available data)
Infections and infestations	Pseudomembranous colitis				
Blood and the lymphatic system disorders		Eosinophilia			Agranulocytosis, Leukopenia, Neutropenia, Thrombocytopenia
Immune system disorders					Anaphylactoid reactions, Drug reaction with eosinophilia and systemic symptoms (DRESS)

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	Frequency not known (cannot be estimated from available data)
Nervous system disorders		Dysgeusia			
Cardiac disorders†		Cardio-respiratory arrest, Hypotension			
Vascular disorders†	Thrombophlebitis				
Gastrointestinal disorders	Diarrhoea, Abdominal pain	Nausea, Vomiting			Oesophagitis‡, Oesophageal ulcer‡
Hepatobiliary disorders	Liver function test abnormal				Jaundice
Skin and subcutaneous tissue disorders	Rash maculo-papular	Urticaria	Erythema multiforme, Pruritus		Toxic epidermal necrolysis, Stevens-Johnson syndrome, Dermatitis exfoliative, Dermatitis bullous, Rash morbilliform, Vaginal infection, Acute Generalised Exanthematous Pustulosis (AGEP)
General disorders and administration site conditions†		Pain, Abscess			Injection site irritation

* CIOMS III categories: Very common ≥ 1/10 (≥ 10%); Common ≥ 1/100 to < 1/10 (≥ 1% and < 10%); Uncommon ≥ 1/1,000 to < 1/100 (≥ 0.1% and < 1%); Rare ≥ 1/10,000 to < 1/1,000 (≥ 0.01% and < 0.1%); Very rare < 1/10,000 (< 0.01%)

† ADRs apply only to injectable formulations

‡ ADRs apply only to oral formulations

4.9 Overdose

In cases of overdosage no specific treatment is indicated.

Significant mortality was observed in mice at an intravenous dose of 855 mg/kg and in rats at an oral or subcutaneous dose of approximately 2618 mg/kg. In the mice, convulsions and depression were observed.

The serum biological half-life of lincomycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis.

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

Microbiology: Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

Aerobic Gram-positive cocci, including:

Staphylococcus aureus;

Staphylococcus epidermidis (*penicillinase and nonpenicillinase producing strains*);

When tested by *in vitro* methods some staphylococcal strains originally resistant to erythromycin rapidly develop resistance to clindamycin;

Streptococci (except *Streptococcus faecalis*);

Pneumococci.

Anaerobic Gram-negative bacilli, including:

Bacteroides species (including *Bacteroides fragilis* group and *Bacteroides melaninogenicus* group);

Fusobacterium species.

Anaerobic Gram-positive non-sporeforming bacilli, including:

Propionibacterium

Eubacterium

Actinomyces species

Anaerobic and microaerophilic Gram-positive cocci, including:

Peptococcus species;

Peptostreptococcus species;

Microaerophilic streptococci.

Clostridia:

Clostridia are more resistant than most anaerobes to clindamycin. Most *Clostridium perfringens* are susceptible, but other species, e.g., *Clostridium sporogenes* and *Clostridium tertium* are frequently resistant to clindamycin.

Susceptibility testing should be done.

Cross resistance has been demonstrated between clindamycin and lincomycin. Antagonism has been demonstrated between clindamycin and erythromycin.

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 300 mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 microgram/ml is achieved within three hours; 600 mg gives 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. 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 sulphoxide 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 **"Special warnings and special precautions for use"** for further information.

5.3 Preclinical safety data

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 Salmonella reversion test. Both tests were negative.

Impairment of fertility:

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

In oral embryo foetal development studies in rats and subcutaneous embryo foetal development studies in rats and rabbits, no developmental toxicity was observed except at doses that produced maternal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol

Disodium edetate

Sodium hydroxide

Water for injection

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 sulphate, phenytoin sodium and ranitidine hydrochloride.

6.3 Shelf-life

24 months

6.4 Special precautions for storage for product and admixture storage

Store refrigerated at 2-8°C.

6.5 Nature and contents of container

Type 1 flint glass ampoule containing 2 ml, 4 ml or 6 ml sterile, aqueous solution, packed in cardboard carton, together with a leaflet.

6.6 Instructions for use/handling

Dalacin C 150 mg/ml (clindamycin 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 sulphate, aztreonam, cefamandole nafate, cephazolin sodium, cefotaxime sodium, cefoxitin sodium, ceftazidime sodium, ceftizoxime sodium, gentamicin sulphate, netilmicin sulphate, piperacillin and tobramycin.

The compatibility and duration of stability of drug admixtures will vary depending upon concentration and other conditions.

MANUFACTURER: Pfizer Manufacturing Belgium NV/SA.

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The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in September 2014