הריני להצהיר כי נערכה בדיקה כפולה של העלון ,במסגרתה העלון נקרא מתחילתו ועד סופו .למיטב הבנתי אין בו סתירות ,שגיאות כתיב ,תחביר או טעויות בתוכנו והוא תואם לתנאי הרישום של התכשיר בישראל .הריני להצהיר בזאת כי השינויים המסומנים בעלון זה הנם השינויים היחידים שבוצעו" .

"הצעת העלון/עדכון/ החמרה המוגשת ,אומצה כלשונה מלבד התאמה לתנאי הרישום בישראל והפורמט, ככל שנדרש מהאסמכתא הבאה: **UK SPC** כפי שאושרה במדינה: **UK** בתאריך: **מרץ 2020**"

הצעת העלון עונה לדרישות חוזר " מסלול הודעה (נוטיפיקציה) לעדכון עלונים של תכשירים הומניים ווטריניריים עדכון דצמבר – "2019, זאת בנוסף להצהרות בהתאם לדרישות סעיף 5.8.6 בנוהל "הנחיות להגשת עדכון עלונים לרופא ולצרכן."

Pfizer Pharmaceuticals Israel Ltd.
Oshrit Eshet
Approved Pharmacist
License 37185
28/06/2020

DALACIN® C 150MG/ML

SUMMARY OF PRODUCT CHARACTERISTICS

1. 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.

Excipients with known effect:

Each ml of solution contains 9mg of benzyl alcohol see sections 4.3 and 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

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

Posology
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.

Paediatric population
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. See *Precautions* for other factors which should be taken into consideration

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 Contraindications

Dalacin® C 150mg/ml 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.

Dalacin® C 150mg/ml 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 special precautions for use

Warnings

The clindamycin phosphate injectable formulation contains benzyl alcohol (9mg/ml). Intravenous administration of the preservative benzyl alcohol has been associated with serious adverse events, and death in paediatric patients including neonates characterized by central nervous system depression, metabolic acidosis, gasping respirations, cardio-vascular failure and haematological anomalies ("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. Use only if it is necessary and if there are no alternatives possible. If given in high volumes, should be used with caution and preferably for short term treatment in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis) due to benzoic acid (a metabolite of benzyl alcohol).

Premature and low-birth weight infants may be more likely to develop toxicity.
Benzyl alcohol containing products should not be used in pre-term or full-term neonates unless strictly necessary.

Benzyl alcohol can cross the placenta and clindamycin should only be used during pregnancy if clearly needed (see section 4.6).

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 150mg/ml 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 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. 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 diarrhea 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 150mg/ml 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.

The use of clindamycin phosphate may result in overgrowth of non-susceptible organisms, particularly yeasts.

Prolonged administration of Dalacin® C 150mg/ml, 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 150mg/ml in atopic individuals.

Dalacin® C 150mg/ml 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.

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.

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

~~Lactation~~

Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from 0.7 to 3.8 µg/ml. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers

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

Dalacin® C 150mg/ml 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)

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		cardio-respiratory 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*,
General Disorders and Administrative Conditions		pain†, injection site abscess†			injection site irritation†*
Investigations	liver function				

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)
	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.Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

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

Pharmacotherapeutic group: Lincocosamide antibiotics, ATC Code J01FF01.

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 (MLSB) 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 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 fetal 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 "**Special warnings and special precautions for use**" for further information.

5.3 Preclinical safety data

Impairment of fertility
Fertility studies in rats treated orally with up to 300 mg/kg/day (2-fold the human exposure based on mg/m2) revealed no effects on fertility or mating ability.

Pregnancy
In oral embryo-fetal development studies in rats and subcutaneous embryo-fetal development studies in rats and rabbits, embryo-fetal 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-fetal 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~~None stated~~

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Disodium edetate
Sodium hydroxide
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

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store refrigerated at 2-8°C. Do not freeze.

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.

Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

Dalacin® C 150mg/ml 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. MANUFACTURER

Pfizer Manufacturing Belgium NV/SA, 2870 Puurs, Belgium.

8. LICNESE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

9. LICENSE NUMBER

125-21-21164

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~~The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by the Ministry of Health in September 2014 and updated according to the guidelines of the Ministry of Health in March 2020~~

טבלת מעקב עדכון עלון לרופא

הערות	אסמכתא לעדכון	פרקים שהתעדכנו	תאריך עדכון העלון
	UK SPC last updated 03/2020 Version DA_24 inj UK	Full alignment to UK SPC	31/03/2020
	Reg SPC DA 25_1 Inj UK (effective 31/03/2020)	5.3	June 2020