DALACIN® C CAPSULES 150 MG
DALACIN® C CAPSULES 300MG

NAME OF THE MEDICINAL PRODUCT

Dalacin® C Capsules 150 mg
Dalacin® C Capsules 300 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 150mg or 300mg of clindamycin.
Each capsule contains lactose.
For the full list of excipients, see section Description (8) in this leaflet.

PHARMACEUTICAL FORM

Capsules.To reduce the development of drug-resistant bacteria and maintain the effectiveness of Dalacin C Capsules and other antibacterial drugs, Dalacin C Capsules should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING

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

Because Dalacin C Capsules 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 AND USAGE** 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 diaarrhea following antibacterial drug 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 antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

1. INDICATIONS AND USAGE

Therapeutic Indication
Treatment of infections caused by susceptible strains of anaerobic microorganisms.

Additional Therapeutic Activity

Treatment of Malaria

2. DOSAGE AND ADMINISTRATION

Administer Dalacin C Capsules with a full glass of water (approximately 200 to 250 mL) and at least 30 minutes before lying down to reduce the potential for esophageal irritation (See section 6).

Dosage in Adults
Clindamycin hydrochloride capsules (oral administration):
600-1800 mg/day divided in 2, 3 or 4 equal doses.

Dosage in Children (over 1 month of age)
Clindamycin hydrochloride capsules (oral administration):
To avoid the possibility of esophageal irritation, clindamycin HCl capsules should be taken with a full glass of water and no less than 30 minutes before lying down.Doses of 8-25 mg/kg/day in 3 or 4 equal doses.

Dosage in Elderly
Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration. Therefore, dosage adjustments are not necessary in the elderly with normal hepatic function and normal (age-adjusted) renal function (see Section 4.2 Pharmacokinetic Properties).

Dosage in Renal Impairment
Clindamycin dosage modification is not necessary in patients with renal insufficiency.

Dosage in Hepatic Impairment
Clindamycin dosage modification is not necessary in patients with hepatic insufficiency.

Dosage in Specific Indications
(a) Treatment of Beta-Hemolytic Streptococcal Infections
Refer to the dosage recommendations above. Treatment should be continued for at least 10 days.

(b) Treatment of Chlamydia trachomatis Cervicitis
Clindamycin hydrochloride capsules orally 450-600 mg 4 times daily for 10-14 days .

(c) Treatment of Toxoplasmic Encephalitis in Patients with AIDS

Clindamycin hydrochloride orally 600-1200 mg every 6 hours for 2 weeks followed by 300-600 mg orally every 6 hours. The usual total duration of therapy is 8 to 10 weeks. The dose of pyrimethamine is 25 to 75 mg orally each day for 8 to 10 weeks. Folinic acid 10 to 20 mg/day should be given with higher doses of pyrimethamine.

(d) Treatment of Pneumocystis carinii Pneumonia in Patients with AIDS
Clindamycin hydrochloride 300 to 450 mg orally every 6 hours for 21 days, and Primaquine 15 to 30 mg dose orally once daily for 21 days.

(e) Treatment of Acute Streptococcal Tonsillitis/Pharyngitis
Clindamycin hydrochloride capsules 300 mg orally twice daily for 10 days.

(f) Dosage for Additional Therapeutic Activity - Treatment of Malaria:

Uncomplicated Malaria/P falciparum

Adults:

Quinine sulfate: 650 mg orally three times daily for 3 or 7 days plus clindamycin: 20 mg base/kg/day orally divided three times daily for 7 days.

Children:

Quinine sulfate: 10 mg/kg orally three times daily for 3 or 7 days plus clindamycin: 20 mg base/kg/day orally divided three times daily for 7 days.

Severe malaria

Adults:
Quinidine gluconate: 10 mg/kg loading dose IV over 1-2 hrs, then 0.02 mg/kg/min continuous infusion for at least 24 hours (for alternative dosing regimen please refer to quinidine label). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above, plus clindamycin: 20 mg base/kg/day orally divided three times daily for 7 days. If patient not able to take oral medication, give 10 mg base/kg clindamycin loading dose IV followed by 5 mg base/kg IV every 8 hours. Avoid rapid IV administration. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. Treatment course = 7 days.

Children:

Quinidine gluconate: Same mg/kg dosing and recommendations as for adults plus clindamycin: 20 mg base/kg/day orally divided three times daily for 7 days. If patient not able to take oral medication, give 10 mg base/kg clindamycin loading dose IV followed by 5 mg base/kg IV every 8 hours. Avoid rapid IV administration. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. Treatment course = 7 days.

(g) Prophylaxis of Endocarditis in Patients Sensitive to Penicillin
Clindamycin hydrochloride capsules (oral administration). Adults: 600 mg 1 hour before procedure; children: 20 mg/kg 1 hour before procedure.

3. CONTRAINDICATIONS

Dalacin C Capsules is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin or to any of the excipients listed in the section 8.

4. WARNINGS

4.1 See **BOXED WARNING**

***Clostridioides difficile* Associated Diarrhea**

Clostridioides difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Dalacin C Capsules, and may range in severity from mild diarrhea 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 diarrhea following antibacterial drug 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 antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

4.2 Anaphylactic and Severe Hypersensitivity Reactions

Anaphylactic shock and anaphylactic reactions have been reported (see **ADVERSE REACTIONS**).

Severe hypersensitivity reactions, including severe skin reactions such as toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and Kounis syndrome some with fatal outcome, have been reported (see **ADVERSE REACTIONS**).

In case of such an anaphylactic or severe hypersensitivity reaction, discontinue treatment permanently and institute appropriate therapy.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens.

4.3 Nephrotoxicity

Clindamycin is potentially nephrotoxic and cases with acute kidney injury have been reported. Consider monitoring of renal function particularly in patients with pre-existing renal dysfunction or those taking concomitant nephrotoxic drugs. In case of acute kidney injury, discontinue Dalacin C Capsules when no other etiology is identified.

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

5. PRECAUTIONS

5.1 General
Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency.

Dalacin C Capsules should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Dalacin C Capsules should be prescribed with caution in atopic individuals.

Indicated surgical procedures should be performed in conjunction with antibacterial drug therapy.

The use of Dalacin C Capsules occasionally results in overgrowth of nonsusceptible organisms—particularly yeasts. Should superinfections occur, appropriate measures should be taken as indicated by the clinical situation.

Clindamycin dosage modification is not necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of clindamycin half-life has been found. However, it was postulated from studies that when given every eight hours, accumulation should rarely occur. Therefore, dosage modification in patients with liver disease may not be necessary. However, periodic liver enzyme determinations should be made when treating patients with severe liver disease.

Prescribing Dalacin C Capsules in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Due to the risk of esophagitis and esophageal ulcer, it is important to ensure adherence with administration guidance (See section 2 & section 6).

5.2 Laboratory Tests
During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed.

5.3 Drug Interactions
Clindamycin 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.

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 increase plasma concentrations of clindamycin and inducers of these isoenzymes may reduce plasma concentrations of clindamycin. In the presence of strong CYP3A4 inhibitors, monitor for adverse reactions. 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.

5.4 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential. Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.6 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

5.5 Pregnancy: Teratogenic effects

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.

Clindamycin should be used during the first trimester of pregnancy only if clearly needed. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy. Because animal reproduction studies are not always predictive of the human response, this drug should be used during pregnancy only if clearly needed.

Reproduction studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (3.2 and 1.6 times the highest recommended adult human dose based on

mg/m^2, respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (1.3 and 0.7 times the highest recommended adult human dose based on mg/m^2, respectively) revealed no evidence of teratogenicity.

5.6 Nursing Mothers
Limited published data based on breast milk sampling reports that clindamycin appears in human breast milk in the range of less than 0.5 to 3.8 mcg/mL. Clindamycin has the potential to cause adverse effects on the breast-fed infant's gastrointestinal flora. 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. Monitor the breast-fed infant for possible adverse effects on the gastrointestinal flora, such as diarrhea, candidiasis (thrush, diaper rash) or rarely, blood in the stool indicating possible antibacterial drug-associated colitis.

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 breast-fed child from clindamycin or from the underlying maternal condition.

5.7 Pediatric Use
When Dalacin C Capsules is administered to the pediatric population, appropriate monitoring of organ system functions is desirable.

5.8 Geriatric Use
Clinical studies of clindamycin did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. However, other reported clinical experience indicates that antibacterial drug-associated colitis and diarrhea (due to *Clostridioides difficile*) seen in association with most antibacterial drug occur more frequently in the elderly (>60 years) and may be more severe. These patients should be carefully monitored for the development of diarrhea.

Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration.

5.9 Important information regarding some of the ingredients of the medicine
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine,

6. ADVERSE REACTIONS
The following reactions have been reported with the use of clindamycin.

Infections and Infestations: *Clostridium difficile* colitis

Gastrointestinal: Abdominal pain, pseudomembranous colitis, nausea, vomiting, and diarrhea (see **BOXED WARNING**). The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see **WARNINGS**). Esophagitis and esophageal ulcer have been reported, particularly when taken in a lying position or with a small amount of water. An unpleasant or metallic taste has been reported after oral administration.

Hypersensitivity Reactions: Generalized mild to moderate morbilliform-like (maculopapular) skin rashes are the most frequently reported adverse reactions. Vesiculobullous rashes, as well as urticaria, have been observed during drug therapy. Severe skin reactions such as toxic epidermal necrolysis, some with fatal outcome, have been reported (See **WARNINGS**). Cases of acute generalized exanthematous pustulosis (AGEP), erythema multiforme, some resembling Stevens-Johnson syndrome, anaphylactic shock, anaphylactic reaction, Kounis syndrome (acute myocardial ischemia with or without myocardial infarction may occur as part of an allergic reaction), cutaneous vasculitis,
symmetrical drug-related intertriginous and flexural exanthema, and hypersensitivity have also been reported.

Skin and Mucous Membranes: Pruritus, vaginitis, angioedema and rare instances of exfoliative dermatitis have been reported. (See **Hypersensitivity Reactions**.)

Liver: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Renal: Acute Kidney Injury (See **WARNINGS**) .

Hematopoietic: Transient neutropenia (leukopenia) and eosinophilia have been reported. Reports of agranulocytosis and thrombocytopenia have been made. No direct etiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Immune System: Drug reaction with eosinophilia and systemic symptoms (DRESS) cases have been reported.

Musculoskeletal: Cases of polyarthritis have been reported.

Reporting suspected adverse reactions after authorization 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/

7. OVERDOSAGE

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.

Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

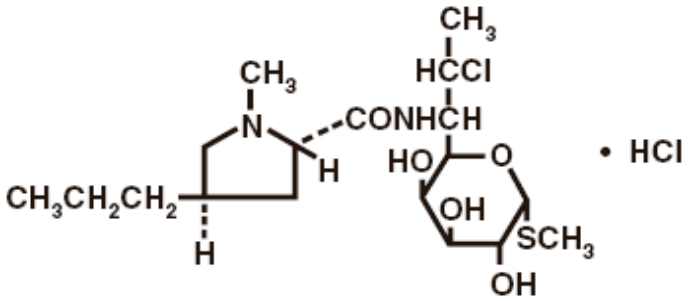
8. DESCRIPTION

Clindamycin hydrochloride is the hydrated hydrochloride salt of clindamycin. Clindamycin is a semisynthetic antibacterial drug produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

Dalacin C Capsules contain clindamycin hydrochloride equivalent to 150 mg or 300 mg of clindamycin.

Inactive ingredients:
Dalacin C Capsules 150 mg: Maize starch, lactose, magnesium stearate, talc, titanium dioxide (E171) and gelatin.
Dalacin C Capsules 300 mg : Maize starch, lactose, magnesium stearate, talc, titanium dioxide (E171), erythrosine (E127), indigo carmine (E132) and gelatin.

The structural formula is represented below:



The chemical name for clindamycin hydrochloride is Methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-*galacto*-octopyranoside monohydrochloride.

9. CLINICAL PHARMACOLOGY

Human Pharmacology

Absorption

Pharmacokinetic studies with a 150 mg oral dose of clindamycin hydrochloride in 24 normal adult volunteers showed that clindamycin was rapidly absorbed after oral

administration. An average peak serum concentration of 2.50 mcg/mL was reached in 45 minutes; serum concentrations averaged 1.51 mcg/mL at 3 hours and 0.70 mcg/mL at 6 hours. Absorption of an oral dose is virtually complete (90%), and the concomitant administration of food does not appreciably modify the serum concentrations; serum concentrations have been uniform and predictable from person to person and dose to dose. Pharmacokinetic studies following multiple doses of CLEOCIN HCl for up to 14 days show no evidence of accumulation or altered metabolism of drug. Doses of up to 2 grams of clindamycin per day for 14 days have been well tolerated by healthy volunteers, except that the incidence of gastrointestinal side effects is greater with the higher doses.

Distribution
Concentrations of clindamycin in the serum increased linearly with increased dose. Serum concentrations exceed the MIC (minimum inhibitory concentration) for most indicated organisms for at least six hours following administration of the usually recommended doses. Clindamycin is widely distributed in body fluids and tissues (including bones). No significant concentrations of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges.

Metabolism
In vitro studies in human liver and intestinal microsomes indicated that clindamycin is predominantly metabolized by Cytochrome P450 3A4 (CYP3A4), with minor contribution from CYP3A5, to form clindamycin sulfoxide and a minor metabolite, N-desmethylclindamycin.

Excretion
The average biological half-life is 2.4 hours. Approximately 10% of the bioactivity is excreted in the urine and 3.6% in the feces; the remainder is excreted as bioinactive metabolites.

Specific Populations
Patients with Renal Impairment/Hepatic Impairment
The elimination half-life of clindamycin is increased slightly in patients with markedly reduced renal or hepatic function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

Geriatric Patients
Pharmacokinetic studies in elderly volunteers (61–79 years) and younger adults (18–39 years) indicate that age alone does not alter clindamycin pharmacokinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentration-time curve) after IV administration of clindamycin phosphate. After oral administration of clindamycin hydrochloride, the average elimination half-life is increased to approximately 4.0 hours (range 3.4–5.1 h) in the elderly compared to 3.2 hours (range 2.1 – 4.2 h) in younger adults. The extent of absorption, however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function[1].

Obese Pediatric Patients Aged 2 to Less than 18 Years and Obese Adults Aged 18 to 20 Years
An analysis of pharmacokinetic data in obese pediatric 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.

Microbiology

Mechanism of Action
Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is bacteriostatic.

Resistance
Resistance to clindamycin is most often caused by modification of specific bases of the 23S ribosomal RNA. Cross-resistance between clindamycin and lincomycin is complete. Because the binding sites for these antibacterial drugs overlap, cross-resistance is sometimes observed among lincosamides, macrolides and streptogramin B. Macrolide-inducible resistance to clindamycin occurs in some isolates of macrolide-resistant bacteria. Macrolide-resistant isolates of staphylococci and beta-hemolytic streptococci should be screened for induction of clindamycin resistance using the D-zone test.

Antimicrobial Activity
Clindamycin has been shown to be active against most of the isolates of the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*:
Gram-positive bacteria
Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Anaerobic bacteria
Clostridium perfringens
Fusobacterium necrophorum
Fusobacterium nucleatum
Peptostreptococcus anaerobius
Prevotella melaninogenica

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for clindamycin against isolates of a similar genus or organism group. However, the efficacy of clindamycin in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.
Gram-positive bacteria
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae

Streptococcus anginosus
Streptococcus mitis
Streptococcus oralis

Anaerobic bacteria
Actinomyces israelii
Clostridium clostridioforme
Eggerthella lenta
Finegoldia (Peptostreptococcus) magna
Micromonas (Peptostreptococcus) micros
Prevotella bivia
Prevotella intermedia
Propionibacterium acnes

10. HOW SUPPLIED/STORAGE AND HANDALING

Nature and Contents of Container

Dalacin C 150mg – Blisters containing 16 or 100 capsules.
Dalacin C 300mg – Blisters containing 16 or 100 capsules.

Shelf-life
The expiry date of the product is indicated on the packaging materials.
Special Precautions for Storage
Store at room temperature, below 25°C.

11. LICENSE MARKETING HOLDER:

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

12. LICENSE NUMBER:

Dalacin C Capsules 150mg 019-95-24895
Dalacin C Capsules 300mg 105-03-28594

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