DALACIN C - Oral Capsules

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

   Active Ingredient: Clindamycin hydrochloride.
   Inactive ingredients: Magnesium stearate, maize starch, talc, lactose, hard gelatin capsule (titanium dioxide, gelatin, 300 mg only- erythrosine, indigo carmine).

   Clindamycin is a semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent compound lincomycin.

   Clindamycin hydrochloride is the hydrated hydrochloride salt of clindamycin. Each capsule contains clindamycin hydrochloride equivalent to 150 mg or 300 mg of clindamycin.

2. PHARMACEUTICAL FORM

   Capsules.

3. CLINICAL PARTICULARS

   3.1.1 Therapeutic Indications

   Treatment of infections caused by susceptible strains of anaerobic microorganisms.

   3.1.2 Additional Therapeutic Activity

   Treatment of Malaria

   3.2 Posology and Method of Administration

   Dosage in Adults
   Clindamycin hydrochloride capsules (oral administration):
   600-1800 mg/day divided in 2, 3 or 4 equal doses. To avoid the possibility of esophageal irritation, clindamycin HCl capsules should be taken with a full glass of water.

   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.
   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.

3.3 Contraindications

Clindamycin is contraindicated in patients previously found to be sensitive to clindamycin or lincomycin or to any component of the formulation.

3.4 Special Warnings and Special Precautions for Use

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider the diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of “antibiotic-associated colitis”. 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 diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, 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 antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

Caution should be used when prescribing Dalacin C to individuals with a history of gastrointestinal disease, especially colitis.
If therapy is prolonged, liver and kidney function tests should be performed.

Prolonged administration of Dalacin C, as with any anti infective, may result in super infection due to organisms resistant to clindamycin.

3.5 Interaction with Other Medicaments and Other Forms of Interaction

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

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.

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.

3.6 Pregnancy and Lactation

Use in 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. 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. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.

3.7 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.

3.8 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common ≥ 1/100 to &lt; 1/10</th>
<th>Uncommon ≥ 1/1000 to &lt; 1/100</th>
<th>Rare ≥ 1/10000 to &lt; 1/1000</th>
<th>Very Rare &lt; 1/10000</th>
<th>Frequency not known (cannot be estimated from available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Pseudomembranous colitis</td>
<td></td>
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<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Eosinophilia</td>
<td></td>
<td></td>
<td></td>
<td>Agranulocytosis, Leukopenia, Neutropenia, Thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anaphylactoid reactions, Drug reaction with eosinophilia and systemic symptoms (DRESS)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dysgeusia</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea, Abdominal pain</td>
<td>Nausea, Vomiting</td>
<td></td>
<td></td>
<td>Oesophagitis, Oesophageal ulcer</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Liver function test abnormal</td>
<td></td>
<td></td>
<td></td>
<td>Jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash maculopapular</td>
<td>Urticaria</td>
<td>Erythema multiforme, Pruritus</td>
<td></td>
<td>Toxic epidermal necrolysis, Steven Johnson syndrome, Dermatitis exfoliative, Dermatitis bullous, Rash morbilliform, Vaginal infection, Acute Generalised Exanthematous Pustulosis (AGEP)</td>
</tr>
</tbody>
</table>

* CIOMS III categories: Very Common ≥ 1/10 (≥ 10%); Common ≥ 1/100 to < 1/10 (≥ 1% and < 10%); Uncommon ≥ 1/1000 to < 1/100 (≥ 0.1% and < 1%); Rare ≥ 1/10,000 to < 1/1000 (≥ 0.01% and < 0.1%); Very Rare < 1/10,000 (< 0.01%)
**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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: [http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il](http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

### 3.9 Overdose

In cases of overdosage no specific treatment is indicated.

The serum biological half life of clindamycin 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.

### 4. PHARMACOLOGICAL PROPERTIES

#### 4.1 Pharmacodynamic Properties

Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Most Gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

**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.

### 4.2 Pharmacokinetic Properties

Serum level 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 level of 2.50 mcg/mL was reached in 45 minutes; serum levels 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 levels have been uniform and predictable from person to person and dose to dose. Serum level studies following multiple doses of clindamycin hydrochloride for up to 14 days show no evidence of accumulation or altered metabolism of drug. Serum half-life of clindamycin is increased slightly in patients with markedly reduced renal function. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Concentrations of clindamycin in the serum increased linearly with increased dose. Serum levels 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). 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. 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. No significant levels of clindamycin are attained in the cerebrospinal fluid, even in the presence of inflamed meninges. 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, 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.

### 4.3 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/m²) revealed no effects on fertility or mating ability.

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

5. PHARMACEUTICAL PARTICULARS

5.1 Shelf-life

60 months.

5.2 Special Precautions for Storage

Store at room temperature, below 25°C.

5.3 Nature and Contents of Container

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

Manufacturer: PFIZER PGM, FRANCE
License Holder: Pfizer Pharmaceuticals Israel Ltd.

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in August 2015.