1.0 Therapeutic Category

Anti-Infective

2.0 DESCRIPTION

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

Clindamycin Phosphate is a water soluble ester of clindamycin and phosphoric acid. The chemical name of clindamycin phosphate is L-threo-α-D-galacto-Octopyranoside, methyl 7-chloro-6,7,8-trideoxy-6-[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl] amino]-1-thio-, 2-(dihydrogen phosphate), (2S-trans)-.

The molecular formula is C_{18}H_{34}CIN_{2}O_{8}PS and the molecular weight is 504.96.

The structural formula is represented below:

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

The structural formula is represented below:

Clindamycin palmitate hydrochloride is a water soluble salt of the ester of clindamycin and palmitic acid. The chemical name for clindamycin palmitate hydrochloride is Methyl 7-chloro-6, 7, 8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinocarboxamido)-1-thio-L-threo-α-D-galacto-octopyranoside 2-palmitate monohydrochloride.

The structural formula is represented below:
3.0 FORMULATION

Dalacin C 150 mg/mL Sterile Solution for Injection: Each 4 mL contains clindamycin phosphate equivalent to 600 mg of clindamycin.

Dalacin C 150 mg and 300 mg Capsules: Each capsule contains Clindamycin hydrochloride hydrate equivalent to 150 mg and 300 mg of Clindamycin respectively.

Dalacin C Granules for Solution: When reconstituted with water, each 5 mL (1 teaspoonful) of solution contains clindamycin palmitate HCl equivalent to 75 mg of clindamycin.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clindamycin has been shown to be effective in the treatment of the following infections when caused by susceptible anaerobic bacteria or susceptible strains of gram positive aerobic bacteria such as streptococci, staphylococci, pneumococci and susceptible strains of Chlamydia Trachomatis.

1. Upper respiratory infections\(^1\)-\(^4\) including tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever.
2. Lower respiratory infections\(^5\)-\(^9\) including bronchitis, pneumonia, emphysema and lung abscess.
3. Skin and soft tissue infections\(^7\)-\(^9\) including acne, furuncles, cellulites, impetigo, abscesses, and wound infections. For specific skin and soft tissue infections like erysipelas and paronychia (panaritium, it would seem logical that these conditions would respond very well to Dalacin C therapy.
4. Bone and joint infections\(^10\)-\(^11\) including osteomyelitis and septic arthritis.
5. Gynecological infections\(^5\),\(^12\),\(^13\) including endometritis, cellulites, vaginal cuff infection, tubo-ovarian abscess, salpingitis and pelvic inflammatory disease when given in conjunction with an antibiotic of appropriate gram negative aerobic spectrum in cases of cervicitis due to Chlamydia trachomatis, single drug therapy with clindamycin has been shown to be effective in eradicating the organism.
6. Intra-abdominal infections\(^14\),\(^15\) including peritonitis and abdominal abscesses when given in conjunction with an antibiotic of appropriate gram-negative spectrum.
7. Septicemia and endocarditis - The effectiveness of Dalacin C in the treatment of selected cases of endocarditis has been documented when Dalacin C is determined to be bactericidal to the infecting organisms by in vitro testing of appropriate achievable serum concentrations.
8. Dental infection such as periodontal abscess and periodontitis.
9. Toxoplastic encephalitis in patients with AIDS. In patients who are intolerant to conventional treatment, clindamycin in combination with pyrimethamine has been shown to be efficacious.
10. *Pneumocystis jiroveci* (previously classified as *Pneumocystis carinii*) pneumonia in patients with AIDS. In patients who are intolerant to, or do not respond adequately to conventional treatment, clindamycin may be used in combination with primaquine.
11. Malaria, including multi-resistant *Plasmodium falciparum*, or in combination with quinine or chlorquine.
12. Prophylaxis of endocarditis in patients sensitive/allergic to penicillin(s).
13. Prophylaxis of infection in neck and head surgery. Clindamycin phosphate, diluted in normal saline, is used as an intraoperative irritant of the surgical field.

Clindamycin phosphate when used concurrently with an aminoglycoside antibiotic such as gentamycin or tobramycin, has been shown to be effective in preventing peritonitis or intra-abdominal abscess after bowel perforation and bacterial contamination secondary to trauma.

In vitro susceptibility to clindamycin has been shown for the following organisms: *B. melaninogenicus, B. disiens, B. bivius, Peptostreptococcus* spp., *G. vaginalis, M. mullieris, M. curtisii,* and *Mycoplasma hominis.*

### 4.2 Dosage and Method of Administration

**Dosage in Adults**

**Clindamycin phosphate (IM or IV administration):**

The usual daily adult dosage of clindamycin phosphate for infections of the intraabdominal area, female pelvis, and other complicated or serious infections is 2400-2700 mg given in 2, 3, or 4 equal doses. Less complicated infections due to more susceptible microorganisms may respond to lower doses such as 1200-1800 mg/day administered in 3 or 4 equal doses.

Doses of up to 4800 mg daily have been used successfully.

Single IM doses of greater than 600 mg are not recommended.

**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 phosphate (IM or IV administration):

20-40 mg/kg/day in 3 or 4 equal doses.

Clindamycin hydrochloride capsules or clindamycin palmitate solution (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.

In children weighing 10 kg or less, 1/2 teaspoon (37.5 mg) of clindamycin palmitate solution three times a day should be considered the minimum recommended dose.

Dosage in Neonates (under 1 month of age)

Clindamycin phosphate (IM or IV administration): 15-20 mg/kg/day in 3 or 4 equal doses. The lower dosage may be adequate for small premature infants.

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 5.2 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) **Inpatient Treatment of Pelvic Inflammatory Disease**

Clindamycin phosphate 900 mg (IV) every 8 hours daily plus an antibiotic with an appropriate gram negative aerobic spectrum administered IV, e.g., gentamicin 2.0 mg/kg followed by 1.5 mg/kg every 8 hours daily in patients with normal renal function. Continue (IV) drugs for at least 4 days and at least 48 hours after the patient improves. Then continue oral clindamycin hydrochloride 450-600 mg q6h daily to complete 10-14 days total therapy.

(c) **Treatment of Chlamydia trachomatis Cervicitis**

Clindamycin hydrochloride capsules orally 450-600 mg 4 times daily for 10-14 days.

(d) **Treatment of Toxoplastic Encephalitis in Patients with AIDS**

Clindamycin phosphate IV or 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.

(e) **Treatment of Pneumocystis carinii Pneumonia in Patients with AIDS**

Clindamycin phosphate IV 600 to 900 mg every 6 hours or 900 mg IV every 8 hours or 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.

(f) **Treatment of Acute Streptococcal Tonsillitis/Pharyngitis**

Clindamycin hydrochloride capsules 300 mg orally twice daily for 10 days.
(g) **Treatment of Malaria**

Clindamycin hydrochloride capsules or clindamycin palmitate solution (oral administration). Adults: 10 to 20 mg/kg/day and children 10 mg/kg/day administered in equal doses every 12 hours for 7 days, alone, or in combination with quinine (12 mg/kg every 12 hours), or chloroquine (15 to 25 mg every 24 hours), for 3-5 days.

(h) **Prophylaxis of Endocarditis in Patients Sensitive to Penicillin**

Clindamycin hydrochloride capsules or clindamycin palmitate solution (oral administration). Adults: 600 mg 1 hour before procedure; children: 20 mg/kg 1 hour before procedure. Alternatively, when parenteral administration is required: clindamycin phosphate 600 mg IV 1 hour before procedure.

(i) **Prophylaxis of Infection in Head and Neck Surgery**

Clindamycin phosphate 900 mg diluted in 1000 mL normal saline for use as an intraoperative irrigant in contaminated head and neck surgery prior to wound closure.

**Dilution and IV infusion rates**

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:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Diluent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>50 mL</td>
<td>10 min</td>
</tr>
<tr>
<td>600 mg</td>
<td>50 mL</td>
<td>20 min</td>
</tr>
<tr>
<td>900 mg</td>
<td>50-100 mL</td>
<td>30 min</td>
</tr>
<tr>
<td>1200 mg</td>
<td>100mL</td>
<td>40 min</td>
</tr>
</tbody>
</table>

Administration of more than 1200 mg in a single 1-hour infusion is not recommended.

4.3 **CONTRAINDICATIONS**

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

4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**
The clindamycin phosphate injectable formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal “Gasper Syndrome” in premature infants.

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.

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.

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

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrheal 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.

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 Dosage and Method of Administration.

4.5 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.

### 4.6 Pregnancy and Lactation

**Use in Pregnancy**

Clindamycin crosses the placenta in humans. After multiple doses, amniotic fluid concentrations were approximately 30% of maternal blood concentrations. 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.

### 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

1. **Blood and Lymphatic System Disorders:** 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.
2. **Immune System Disorders:** A few cases of anaphylactoid reactions have been reported.
3. **Nervous System Disorders:** Dysgeusia
4. **Cardiac Disorders:** Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration (see Section 4.2 Dosage and Method of Administration).
5. **Vascular Disorders:** Thrombophlebitis has been reported with IV injection. These reactions can be minimized by deep IM injection and avoidance of indwelling intravenous catheters.
6. **Gastrointestinal Disorders:** Abdominal pain, nausea, vomiting and diarrhea (see Section 4.4 Special Warnings and Precautions for Use), esophagitis and esophageal ulcer with oral preparations.
7. Hepatobiliary Disorders: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

8. Skin Maculopapular rash and urticaria have been observed during drug therapy. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported reactions. Rare instances of erythema multiforme have been associated with clindamycin. Pruritus, vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported. Rare cases of toxic epidermal necrolysis and cases of Stevens-Johnson syndrome have been reported during post-marketing surveillance.

9. General Disorders and Administration Site Conditions: Local irritation, pain, abscess formation have been seen with IM injection.

4.9 Overdose

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

5.0 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-sporforming 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

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.
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 micronucleous 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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date of the product.

6.2 Incompatibilities

(This list may not be all-inclusive due to the multiple factors influencing drug compatibility data).

When combined with clindamycin phosphate in an infusion solution, ampicillin, phenytoin sodium, barbiturates, aminophyllin, calcium gluconate, magnesium sulfate, ceftriaxone sodium, and ciprofloxacin are each physically incompatible with clindamycin phosphate.

6.3 Storage Conditions

Solution for Injection - Do not store above 25 °C. Do not refrigerate or freeze
Capsules – Store at temperatures not exceeding 30 °C
Granules for Oral Solution – Store between 15-30 °C

6.4 Availability
Solution for Injection
Dalacin C Injection is a clear, colorless solution packaged in 4 mL, colorless, flint ampoule.

Capsule
150 mg capsules; Hard gelatin capsule with lavender body and maroon cap. Available as blister pack of 10’s. Box of 100’s
300 mg capsules; Hard gelatin capsule with opaque maroon cap and body. Available as blister pack of 10’s. Box of 100’s

Granules for Solution
Dalacin C Flavored Granules is a free flowing, white, granular with cherry flavor. Available in 30 mL and 60 mL amber bottle.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:

Solution for Injection:
Pfizer Manufacturing Belgium NV
Rijksweg 12, 2870 Puurs, Belgium

Capsules:
PT Pfizer Indonesia
PO Box 2706 Jakarta, Indonesia

Granules for Oral Suspension:
Interphil Laboratories, Inc.
Canlubang Industrial Estate
Bo. Pittland, Cabuyao, Laguna, Philippines

For: Pfizer, Inc.
23/F Ayala Life-FGU Center
6811 Ayala Avenue, Makati City, Philippines

References:


9. Atkinson WH, and Royer GL; Clindamycin palmitate - Pediatric Impetigo: A Comparison of Clindamycin Palmitate b.i.d. (7 and 10 days), q.i.d. (7 and 10 days) and Penicillin V q.i.d. (7 and 10 days). Final Report, The Upjohn Company, October 8, 1973 (9126/083).


