1. NAME OF THE MEDICINAL PRODUCT

DALACIN™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: clindamycin hydrochloride or clindamycin phosphate.

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.

Clindamycin phosphate is a water-soluble ester of clindamycin and phosphoric acid. Each mL contains the equivalent of 150 mg clindamycin, 0.5 mg disodium edetate and 9.45 mg benzyl alcohol added as preservative in each mL.

3. PHARMACEUTICAL FORM

Capsules, Solution for injection.

4. 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 and pneumococci.

1. Upper respiratory infections including tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever.
2. Lower respiratory infections including bronchitis, pneumonia, empyema and lung abscess.
3. Skin and soft tissue infections including acne, furuncles, cellulitis, impetigo, abscesses and wound infections, specific skin and soft tissue infections caused by susceptible organisms like erysipelas and paronychia (panaritium).
4. Bone and joint infections including osteomyelitis and septic arthritis.
5. Gynecological infections including endometritis, cellulitis, vaginal cuff infection, tubo-ovarian abscess, salpingitis, and pelvic inflammatory disease when given in conjunction with an antibiotic of appropriate gram-negative spectrum.
6. Intra-abdominal infections including peritonitis and abdominal abscess when given in conjunction with an antibiotic of appropriate gram-negative spectrum.
7. Septicemia and endocarditis. The effectiveness of clindamycin in the treatment of selected cases of endocarditis has been documented when clindamycin is determined

to be bactericidal to the infecting organism by *in vitro* testing of appropriate achievable serum concentrations.

8. Dental infections such as periodontal abscess and periodontitis.
9. Toxoplasmic 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 jirovecii* (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.

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

Limited data from uncontrolled studies using a variety of doses suggest that clindamycin, either orally or parenterally at a dose of 20 mg/kg/day for a minimum of 5 days is useful alternative therapy when used alone or in combination with quinine or amodiaquine, for the treatment of multi-drug resistant *Plasmodium falciparum* infection.

4.2. Posology and method of administration

Clindamycin phosphate IM administration should be used undiluted.

Clindamycin phosphate IV administration should be diluted (See **DILUTION FOR IV USE AND IV INFUSION RATES** below).

Dosage and route of administration should be determined by the severity of the infection, the condition of the patient, and the susceptibility of the causative micro-organisms.

ADULTS: DOSAGE OF CLINDAMYCIN PHOSPHATE (IM OR IV ADMINISTRATION)
The usual daily adult dosage of clindamycin phosphate for infections of the intra-abdominal 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 micro-organisms 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.

CHILDREN OVER ONE MONTH OF AGE: DOSAGE OF CLINDAMYCIN PHOSPHATE (IM OR IV ADMINISTRATION)
20-40 mg/kg/day in 3 or 4 equal doses. Clindamycin should be dosed based on total body weight regardless of obesity.

NEONATES (UNDER 1 MONTH OF AGE): DOSAGE OF 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.

ADULTS: DOSAGE OF ORAL CLINDAMYCIN HYDROCHLORIDE CAPSULES
600-1800 mg/day divided in 2, 3 or 4 equal doses. To avoid the possibility of esophageal irritation, clindamycin hydrochloride capsules should be taken with a full glass of water and no less than 30 minutes before lying down.

CHILDREN OVER 1 MONTH OF AGE: DOSAGE OF ORAL CLINDAMYCIN HYDROCHLORIDE CAPSULES
Doses of 8-25 mg/kg/day in 3 or 4 equal doses. Clindamycin should be dosed based on total body weight regardless of obesity.

Clindamycin capsules are not suitable for children who are unable to swallow them whole.

To avoid the possibility of esophageal irritation, clindamycin hydrochloride capsules should be taken with a full glass of water and no less than 30 minutes before lying down.

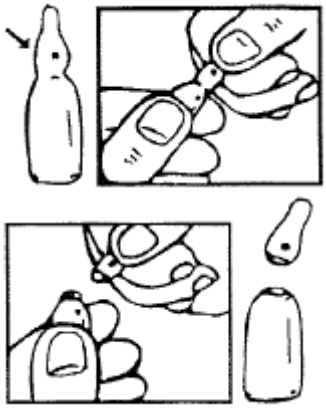
BETA-HEMOLYTIC STREPTOCOCCAL INFECTIONS
In cases of beta-hemolytic streptococcal infections, treatment should be continued for at least 10 days.

ACUTE STREPTOCOCCAL TONSILLITIS/PHARYNGITIS
In the treatment of acute streptococcal tonsillitis/pharyngitis, clindamycin hydrochloride capsules 300 mg may be taken twice daily for 10 days.

TOXOPLASMIC ENCEPHALITIS IN PATIENTS WITH AIDS
Clindamycin phosphate IV or clindamycin hydrochloride by mouth 600-1200 mg every 6 hours for two weeks followed by 300-600 mg by mouth every 6 hours. The usual total duration of therapy is 8 to 10 weeks. The dose of pyrimethamine is 25 to 75 mg by mouth daily for 8 to 10 weeks. Folinic acid 10 to 20 mg/day should be given with higher doses of pyrimethamine.

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 by mouth every 6 hours for 21 days and primaquine 15 to 30 mg dose by mouth once daily for 21 days.

IMPORTANT
No ampoule file is needed to open the ampoules. The neck of the ampoules is prescored at the point of constriction. A colored dot on the ampoule head helps to orientate the ampoule. Take the ampoule and face the colored dot. The ampoule opens easily by placing the thumb on the colored dot and gently pressing downwards as shown.



DILUTION FOR IV USE 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:

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

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

4.3. Contraindications

Clindamycin 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

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 Section 4.3 Contraindications and Section 4.8 Undesirable effects).

The clindamycin phosphate injectable formulation contains benzyl alcohol. The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in pediatric patients. 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. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys’ capacity to detoxify the chemical. Premature and low birth weight infants may be more likely to develop toxicity.

As is the case for almost all antibiotic therapy, clindamycin therapy has been associated with severe colitis, which may end fatally.

The clinical spectrum varies from mild, watery diarrhea to severe, persistent diarrhea, leukocytosis, fever, severe abdominal cramps which may be associated with the passage of blood and mucus which, if allowed to progress, may produce peritonitis, shock and toxic megacolon.

The diagnosis of antibiotic-associated colitis is usually made by the recognition of the clinical symptoms. It can be substantiated by endoscopic demonstration of pseudomembranous colitis and may be further confirmed by culture of the stool for *Clostridioides difficile* on selective media and assay of the stool specimen for the toxin(s) of *C. difficile*.

Onset of antibiotic-associated colitis has occurred during the administration or even two or three weeks following administration of the antibiotic. The disease is likely to take a more severe course in older patients or in patients who are debilitated. In case of occurrence of mild antibiotic-associated colitis, discontinuance of clindamycin is recommended. Treatment with cholestyramine and colestipol resins is recommended as these products have been shown to bind the toxin *in vitro*. The suggested dose of colestipol is 5 g three times daily, and the suggested dose of cholestyramine is 4 g three times daily. When severe antibiotic-associated colitis occurs, this has to be treated with appropriate fluid, electrolyte and protein supplementation.

Studies have also indicated that a toxin(s) produced by Clostridia (especially *C. difficile*) is (are) the principal direct cause of antibiotic-associated colitis. These studies also indicated that this toxigenic Clostridioides is usually sensitive *in vitro* to vancomycin. When 125 to 500 mg vancomycin 4 times daily is administered, there is a rapid observed disappearance of the toxin from fecal samples and a coincident clinical recovery from the diarrhea.

In rare cases colitis may reoccur after cessation of vancomycin treatment. Cholestyramine or colestipol resins bind to vancomycin *in vitro*. If both a resin and vancomycin are to be administered concurrently, it may be advisable to separate the time of administration of each drug.

As an alternative therapy oral bacitracin 25,000 units q.i.d. for 7-10 days could be considered. Drugs which cause bowel stasis should be avoided.

Caution should be exercised in prescribing clindamycin doses in patients with a history of GI disease, particularly colitis.

C. 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.

If therapy is prolonged, liver function tests should be performed.

Clindamycin is potentially nephrotoxic. Acute kidney injury including acute renal failure has been reported. Therefore, monitoring of renal function should be considered during therapy of patients with pre-existing renal dysfunction or taking concomitant nephrotoxic drugs and monitoring of renal function should be performed if therapy is prolonged.

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

Intravenous: 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 Posology and method of administration.

Oral capsules: Due to the risk of esophagitis and esophageal ulcer, it is important to ensure compliance with administration guidance (see Sections 4.2 Posology and method of administration and 4.8 Undesirable effects).

Clindamycin phosphate should be administered with caution in atopic individuals.

Clindamycin dosage modification is not necessary in patients with renal disease. In patients with moderate to severe liver disease, prolongation of the half-life of clindamycin has been found, but a pharmacokinetic study has shown that, when given every eight hours, accumulation of clindamycin should rarely occur. Therefore, dosage reduction in liver disease is not considered necessary.

4.5. Interaction with other medicinal products and other forms of interaction

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 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.

Macrolides may induce clindamycin resistance in certain macrolide-resistant strains, therefore clindamycin should not be administered with a macrolide (see Section 5.1 Pharmacodynamic properties).

4.6. Fertility, pregnancy and lactation

Use in Pregnancy
Benzyl alcohol can cross the placenta. See Section 4.4 Special warnings and 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 limited number of pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. However, there are no adequate and well-controlled studies using clindamycin in pregnant women during the first trimester of pregnancy and this drug should be used during pregnancy only if clearly needed.

Use in Nursing Mothers
Clindamycin has been reported to appear in human breast milk in ranges from <0.5 to 3.8 mcg/mL.

Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. 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. 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 breastfed child from clindamycin or from the underlying maternal condition.

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 system organ class (SOC) and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC.

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency Not Known (cannot be estimated from available data)
Infections and infestations	pseudomembranous colitis*			*Clostridioides difficile* colitis*, vaginal infection*
Blood and lymphatic system disorders	eosinophilia			agranulocytosis*, neutropenia*, thrombocytopenia*, leukopenia*
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	diarrhea	abdominal pain, vomiting, nausea		esophageal ulcer*[‡≠], esophagitis*[‡≠]
Hepatobiliary disorders				jaundice*
Skin and subcutaneous tissue disorders	rash maculo-papular	urticaria	erythema multiforme, pruritus	toxic epidermal necrolysis (TEN)*, Stevens-Johnson syndrome (SJS)*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalized exanthematous pustulosis (AGEP)*, angioedema*, dermatitis exfoliative*, dermatitis bullous*, rash morbilliform*
Renal and urinary disorders				acute kidney injury*
General disorders and administration site conditions		pain[†], injection site abscess[†]		injection site irritation*[†]
Investigations	liver function test			

	abnormal			

*ADRs identified post-marketing
†ADRs apply only to injectable formulations
‡ADRs apply only to oral formulations
§Rare instances have been reported following too rapid intravenous administration (see Section 4.2 Posology and method of administration).
≠Possible occurrence of esophagitis and esophageal ulcer, particularly if taken in a lying position and/or with a small amount of water.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of action
Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis. It binds to the 50S ribosomal subunit and affects both ribosome assembly and the translation process. Although clindamycin phosphate is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin. At usual doses, clindamycin exhibits bacteriostatic activity *in vitro*.

Pharmacodynamic effects
Efficacy is related to the time period over which the agent level is above the minimum inhibitory concentration (MIC) of the pathogen (%T/MIC).

Resistance
Resistance to clindamycin is most often due to mutations at the rRNA antibiotic binding site or methylation of specific nucleotides in the 23S RNA of the 50S ribosomal subunit. These alterations can determine *in vitro* cross resistance to macrolides and streptogramins B (MLS_B phenotype). Resistance is occasionally due to alterations in ribosomal proteins. Resistance to clindamycin may be inducible by macrolides in macrolide-resistant bacterial isolates. Inducible resistance can be demonstrated with a disk test (D-zone test) or in broth. Less frequently encountered resistance mechanisms involve modification of the antibiotic and active efflux. There is complete cross resistance between clindamycin and lincomycin. As with many antibiotics, the incidence of resistance varies with the bacterial species and the geographical area. The incidence of resistance to clindamycin is higher among methicillin-resistant staphylococcal isolates and penicillin-resistant pneumococcal isolates than among organisms susceptible to these agents.

Depending on the sensitivity of the micro-organism and the concentration of the antibiotic, clindamycin may be either bactericidal or bacteriostatic.

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

Aerobic bacteria

Gram-positive bacteria
- *Staphylococcus aureus* (methicillin-susceptible isolates)
- Coagulase-negative staphylococci (methicillin-susceptible isolates)
- *Streptococcus pneumoniae* (penicillin-susceptible isolates)
- Beta-hemolytic streptococci groups A, B, C, and G
- Viridans group streptococci
- *Corynebacterium* spp.

Gram-negative bacteria
- *Chlamydia trachomatis*

Anaerobic bacteria

Gram-positive bacteria
- *Actinomyces* spp.
- *Clostridioides* spp. (except *Clostridioides difficile*)
- *Eggerthella (Eubacterium)* spp.
- *Peptococcus* spp.
- *Peptostreptococcus* spp. *(Finegoldia magna, Micromonas micros)*
- *Propionibacterium acnes*

Gram-negative bacteria
- *Bacteroides* spp.
- *Fusobacterium* spp.
- *Gardnerella vaginalis*
- *Prevotella* spp.

Fungi

- *Pneumocystis jirovecii*

Protozoans

- *Toxoplasma gondii*
- *Plasmodium falciparum*

Breakpoints

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 the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Particularly in severe infections or therapy failure microbiological diagnosis with verification of the pathogen and its susceptibility to clindamycin is recommended.

Resistance is usually defined by susceptibility interpretive criteria (breakpoints) established by Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) for systemically administered antibiotics.

Clinical and Laboratory Standards Institute (CLSI) breakpoints for relevant organisms are listed below.

Table 1. CLSI Susceptibility Interpretive Criteria for Clindamycin

Pathogen	**Minimal Inhibitory Concentrations (mcg/mL)**			**Disk Diffusion (Zone Diameters in mm)[a]**		
	S	**I**	**R**	**S**	**I**	**R**
Staphylococcus spp.	≤0.5	1–2	≥4	≥21	15–20	≤14
Streptococcus spp.	≤0.25	0.5	≥1	≥19	16–18	≤15
Anaerobic bacteria[b]	≤2	4	≥8	NA	NA	NA

NA=not applicable; S=susceptible; I=intermediate; R=resistant.
[a]Disk content 2 micrograms of clindamycin.
[b]MIC ranges for anaerobes are based on agar dilution methodology.

A report of "Susceptible" (S) indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" (I) indicates that the result should be considered equivocal, and, if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" (R) indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the usually achievable concentrations; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard clindamycin powder should provide the MIC ranges in Table 2. For the disk diffusion technique using the 2 mcg clindamycin disk the criteria provided in Table 2 should be achieved.

Table 2. CLSI Acceptable Quality Control (QC) Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	Minimum Inhibitory Concentration Range (mcg/mL)	Disk Diffusion Range (Zone Diameters in mm)
Staphylococcus aureus ATCC 29213	0.06–0.25	NA
Staphylococcus aureus ATCC 25923	NA	24–30
Streptococcus pneumoniae ATCC 49619	0.03–0.12	19–25
Bacteroides fragilis ATCC 25285	0.5–2[a]	NA
Bacteroides thetaiotaomicron ATCC 29741	2–8[a]	NA
Eggerthella lenta ATCC 43055	0.06–0.25[a]	NA

NA=Not applicable.
ATCC® is a registered trademark of the American Type Culture Collection.
[a]MIC ranges for anaerobes are based on agar dilution methodology.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are presented below.

Table 3. EUCAST Susceptibility Interpretive Criteria for Clindamycin

	MIC breakpoints (mg/L)		Zone diameter breakpoints (mm)[a]	
Organism	**S≤**	**R>**	**S≥**	**R<**
Staphylococcus spp.	0.25	0.5	22	19
Streptococcus Groups A, B, C and G	0.5	0.5	17	17
Streptococcus pneumoniae	0.5	0.5	19	19
Viridans group streptococci	0.5	0.5	19	19
Gram-positive anaerobes	4	4	NA	NA
Gram-negative anaerobes	4	4	NA	NA
Corynebacterium spp.	0.5	0.5	20	20

[a]Disk content 2 mcg of clindamycin
NA=not applicable; S=susceptible; R=resistant

EUCAST QC ranges for MIC and disk zone determinations are in the table below.

Table 4. EUCAST Acceptable Quality Control (QC) Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	Minimum Inhibitory Concentration Range (mcg/mL)	Disk Diffusion Range (Zone Diameters in mm)
Staphylococcus aureus ATCC 29213	0.06–0.25	23-29
Streptococcus pneumoniae ATCC 49619	0.03–0.125	22-28

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Miscellaneous organisms including:
Plasmodium falciparum and *Pneumocystis jirovecii* (previously classified as *Pneumocystis carinii*) (in combination with primaquine).

The following organisms are generally resistant to clindamycin:
- Aerobic gram-negative bacilli
- *Streptococcus faecalis*
- Nocardia species
- *Neisseria meningitidis*
- Strains of methicillin-resistant ***Staphylococcus aureus*** and strains of ***Haemophilus influenzae*** (depending on the areas where antibiotic resistance is known to occur).

Although clindamycin hydrochloride is active as well *in vivo* as *in vitro*, clindamycin phosphate does not show any *in vitro* effect. However, both substances are *in vivo* rapidly hydrolyzed to the active base.

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.

After IM administration of 600 mg of clindamycin phosphate, peak serum levels of 9 mcg/mL are reached 1-3 hours after administration. After intravenous infusion of 300 mg in 10 min, resp. 600 mg in 20 min, peak serum levels of 7 mcg/mL and 10 mcg/mL respectively are reached at the end of the infusion. Table 5 gives the average peak serum levels after administration of clindamycin phosphate. Clindamycin serum levels can be maintained above the *in vitro* minimum inhibitory concentration (MIC) for the most sensitive micro-organisms by administration of clindamycin phosphate every 8-12 hours in adults and every 6-8 hours in children or by a continuous IV infusion. A constant level is reached after the third dose.

Table 5. Average Peak Serum Levels After Administration of Clindamycin Phosphate

Dose **Adult (post equilibrium)**	**Clindamycin** **mcg/mL**	**Clindamycin phosphate** **mcg/mL**
300 mg i.v. in 10 min. every 8 hours	7	15
600 mg i.v. in 20 min. every 8 hours	10	23
900 mg i.v. in 30 min. every 12 hours	11	29
1200 mg i.v. in 45 min. every 12 hours	14	49
300 mg i.m. in every 8 hours	6	3
600 mg i.m. in every 12 hours	9	3
Dose **Children (first dose) (1)**	**Clindamycin** **mcg/mL**	**Clindamycin phosphate** **mcg/mL**
5-7 mg/kg i.v. in 1 hour	10	

3-6 mg/kg i.m.	4
5-7 mg/kg i.m.	8

(1) Data in this group from patients being treated for infection

Half-life is somewhat increased in patients with markedly reduced renal or hepatic function. Dosage schedule need not be modified in the presence of mild or moderate renal or hepatic disease. 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 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). In bone tissue ±40% (20%-75%) of the serum level is reached, in the mother milk 50%-100%, in the synovial fluid 50%, in sputum 30%-75%, in the peritoneal liquid 50%, in the fetal blood 40%, in the pus 30%, in the pleural liquid 50%-90%. However clindamycin does not penetrate in the liquor cerebrospinalis, even not in case of meningitis.

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 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.

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.

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

DALACIN C™ Capsules 150 mg
Each capsule contains:
Clindamycin (clindamycin hydrochloride) 150 mg - Maize starch - Lactose monohydrate - Talc - Magnesium stearate - Titanium dioxide - Gelatin.

DALACIN C™ Capsules 300 mg
Each capsule contains:
Clindamycin (clindamycin hydrochloride) 300 mg - Maize starch - Lactose monohydrate - Talc - Magnesium stearate - Titanium dioxide - Gelatin.

DALACIN C™ Solution for injection 150 mg/mL
Each 2 mL contains:
Clindamycin (clindamycin phosphate) 150 mg/mL - Benzyl alcohol - Edetate disodium - Water for injection.

DALACIN C™ Solution for injection 150 mg/mL
Each 6 mL contains:
Clindamycin (clindamycin phosphate) 150 mg/mL - Benzyl alcohol - Edetate disodium - Water for injection.

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, aminophylline, calcium gluconate, magnesium sulfate, ceftriaxone sodium, and ciprofloxacin are each physically incompatible with clindamycin phosphate.

6.3. Shelf life

The expiry date (month/year) is mentioned on the package after "EXP" (EXP - expiry date).

6.4. Special precautions for storage

Capsules: Do not store above 30°C.
Solution for injection: Store at 2°C to 8°C (Refrigerate. Do not freeze).

6.5. Nature and contents of container

ORAL ADMINISTRATION
- Capsules:
  - Packages of 100 capsules dosed at 150 mg.
  - Packages of 16 and 100 capsules dosed at 300 mg.

INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION
- Solution for injection:
  - Package of 1 ampoule at a dose of 2 mL.
  - Package of 1 ampoule at a dose of 6 mL.

Not all presentations will be available locally.

6.6. Special precautions for disposal and other handling

Clindamycin phosphate has been known 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, cefazolin 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. PRODUCT OWNER

Pfizer Inc.
New York
United States

DALC-SIN-1023/0
Date of last revision: October 2023