

Clindamycin Capsules I.P.

DALACIN C[®]

Clindamycin Injection I.P.

DALACIN C[®]



1. GENERIC NAME

Clindamycin Capsules I.P.
Clindamycin Injection I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DALACIN C 150 mg – 300 mg capsules

Each hard gelatin capsule contains:

Clindamycin hydrochloride I.P. equivalent to clindamycin 150 mg and 300 mg.

DALACIN C 300 mg sterile solution for injection – 2 ml ampoule and DALACIN C 600 mg sterile solution for injection – 4 ml ampoule

Each ml contains:

Clindamycin phosphate U.S.P. equivalent to clindamycin 150 mg.

List of Excipients

Capsules (150 mg/300 mg):

Magnesium stearate, Maize starch, Talc, Lactose monohydrate

Colour used in 150 mg capsule shell – Titanium dioxide

Colour used in 300 mg capsule shell – Titanium dioxide, Indigocarmine, Erythrosine

Injection (300 mg/600 mg):

Benzyl Alcohol (9.45 mg per ml including 5% overages), Disodium Edetate, Sodium Hydroxide (for pH adjustment), Water for injection.

All strengths/presentations mentioned in this document might not be available in the

market.

3. DOSAGE FORM & STRENGTH

Hard Gelatin Capsules: 150 mg & 300 mg

Injection: 300 mg & 600 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Clindamycin is indicated in the treatment of serious infections, when caused by clindamycin susceptible strains of gram-positive aerobes such as streptococci, pneumococci and staphylococci, or by susceptible anaerobic bacteria (see section 5.2). In cases of aerobic infections clindamycin is an alternative if other antimicrobial drugs are inactive or contraindicated. In cases of anaerobic infections clindamycin can be considered as a first choice drug.

1. Upper respiratory tract infections: chronic sinusitis caused by anaerobic strains. Clindamycin can be used for selected cases of chronic suppurative otitis media or as adjunctive therapy along with an antibiotic active against aerobic gram-negative organisms. Infections caused by *H. influenzae* are not an indication (see section 5.2). Clindamycin can also be used in cases of recurrent pharyngotonsillitis.
2. Lower respiratory tract infections including infectious exacerbation of chronic bronchitis and pneumonia.
3. Serious skin and soft tissue infections caused by susceptible organisms.
4. Bone and joint infections including osteomyelitis and septic arthritis.
5. Serious gynaecological infections of the pelvis including pelvic inflammatory disease (PID). Clindamycin can also be used in a single therapy in cases of cervicitis due to *Chlamydia trachomatis*.
6. Intra-abdominal infections including peritonitis and abdominal abscess. In simultaneous administration associated with a suitable Gram-negative antibiotic such as an aminoglycoside, clindamycin appears to be effective in preventing peritonitis or intra-abdominal abscesses after perforation and bacterial contamination following trauma.
7. Septicaemia and endocarditis.
Selected cases of septicaemia and/or endocarditis due to susceptible organisms have responded well to clindamycin. However, bactericidal drugs are often preferred for these infections.
8. Dental infections including periodontal abscess and periodontitis.
9. Toxoplasmic encephalitis in patient with AIDS. In patients who cannot tolerate the usual treatment, clindamycin may be used in combination with pyrimethamine.
10. *Pneumocystis jirovecii* pneumonia in patients with AIDS. In patients who cannot tolerate the usual treatment, clindamycin may be used in combination with primaquine.

11. Malaria, including multi-resistant *Plasmodium falciparum*, in combination with quinine.
12. Prophylaxis of infection in neck and head surgery. Clindamycin phosphate, diluted in normal saline, is used as an intraoperative irrigant of the surgical field.

Like other antibiotics information regarding the prevention of local resistance as well as the official recommendations regarding prescription of antibiotics must be reviewed before prescribing clindamycin.

4.2 Posology and method of administration

Posology

The posology and the mode of administration should be determined by the seriousness of the infection, the patient's condition and the sensitivity of the disease causing germ.

It is recommended to swallow the capsules with a glass of water in order to avoid irritation of the oesophagus.

Clindamycin phosphate IM administration should be used undiluted.

Clindamycin phosphate IV administration should be diluted (see dilution for IV use and IV infusion rate below).

Adults:

Clindamycin phosphate solution for injection (IM or IV administration):

The usual daily dose of clindamycin phosphate is 2400-2700 mg in 2, 3 or 4 equal doses for intra-abdominal infections, pelvic infections in women and other serious infections, usually combined with a suitable Gram-negative aerobic antibiotic.

Less complicated infections due to more sensitive germs may respond to lower doses of 1200-1800 mg/day, divided in 3 or 4 equal administrations.

Adults were successfully treated with doses up to 4800 mg daily.

Intramuscular administration of more than 600 mg in one administration is not recommended.

Treatment of Pelvic Inflammatory Disease (PID):

Clindamycin phosphate I.V. 900 mg every 8 hours, associated to a suitable Gram-negative spectrum antibiotic (e.g. gentamicin 2 mg/kg, followed by 1.5 mg/kg every 8 hours) in patients with a normal renal function. This treatment should be administered for at least 4 days. From the moment clinical improvement occurs, the treatment should be continued

for another 2 days. Then 1800 mg of clindamycin hydrochloride per day should be administered orally, divided over several administrations, up to a total treatment duration of 10 to 14 days.

Clindamycin hydrochloride capsules (oral administration):

The usual daily dose is 600-1800 mg divided in 3 or 4 administrations.

In the exceptional case of a treatment for recurrent β -haemolytic streptococcal infection: 300 mg, twice daily for at least 10 days.

Cervicitis due to *Chlamydia trachomatis*: 1800 mg per day, divided over several administrations for 10-14 days.

Paediatric population:

Clindamycin phosphate (IM or IV administration) in children older than 1 month:

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

Clindamycin hydrochloride capsules (for children who are able to swallow capsules) in children older than 1 month:

8-25 mg/kg/day in 3 or 4 equal administrations.

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

Dosage in Neonates (younger than 1 month of age)

Clindamycin phosphate (IM or IV administration):

15-20 mg/kg/day in 3 or 4 equal doses. The lowest dose can be indicated for small premature infants.

Daily doses:

10 kg of body weight: 1½ (7,5 ml) to 3 (15 ml) measures

20 kg of body weight: 3 (15 ml) to 6 (30 ml) measures

30 kg of body weight: 4 (20 ml) to 8 (40 ml) measures

Posology in cases of renal and/or liver function impairment:

Dose adjustment is not necessary in patients with an impaired renal function. Haemodialysis and peritoneal dialysis are not effective to remove clindamycin from the blood.

In patients with moderately to seriously reduced liver function, a prolonged half-life of clindamycin was seen. Accumulation is rare if clindamycin is administered every 8 hours. A dose reduction is, therefore, not considered necessary.

Dosage in specific indications:

Toxoplasmic encephalitis in patients with AIDS:

Clindamycin phosphate IV or clindamycin hydrochloride orally in a dose of 600-1200 mg every 6 hours for 2 weeks, followed by oral administration of 300-600 mg every 6 hours. The total treatment usually lasts 8 to 10 weeks. Oral administration of 25 mg to 75 mg of pyrimethamine per day for 8 to 10 weeks is necessary. With higher doses of pyrimethamine one should administer 10 to 20 mg of folic acid per day.

Pneumocystis jirovecii pneumonia in patients with AIDS:

Clindamycin phosphate IV in intravenous infusion in a dose of 600 to 900 mg every 6 hours or Clindamycin phosphate IV in intravenous infusion in a dose of 900 mg every 8 hours or Clindamycin hydrochloride orally in a dose of 300 to 450 mg every 6 hours for 21 days, combined with 15 to 30 mg of oral primaquine per day for 21 days.

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.

Paediatric population:

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 is 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.

Paediatric population:

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.

Prophylaxis of Infection in Head and Neck Surgery

Method of administration

Dilution for IV use and IV infusion rates

The concentration of clindamycin in the dilution medium should not be more than 18 mg per ml and the infusion rate should not be more than 30 mg per minute (See section 4.8). The normal infusion rates are as follows:

<u>Dose</u>	<u>Dilution agent</u>	<u>Time</u>
300 mg	50 ml	10 min
600 mg	50 ml	20 min
900 mg	100 ml	30 min
1200 mg	100 ml	40 min

Intravenous infusions of more than 1200 mg per hour are not recommended.

4.3 Contraindications

Hypersensitivity to the active substance, to lincomycin, to any component of the formulation, or to any of the excipients listed in section 2.

In case of infectious meningitis (see section 4.4).

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 sections 4.3 and 4.8).

The clindamycin phosphate injectable formulation contains benzyl alcohol (9.45 mg/ml). Benzyl alcohol may cause anaphylactoid reactions. Intravenous administration of the

preservative benzyl alcohol has been associated with serious adverse events, and death in paediatric patients including neonates characterized by central nervous system depression, metabolic acidosis, gasping respirations, cardio-vascular failure and haematological anomalies (“gasping syndrome”). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Use only if it is necessary and if there are no alternatives possible. If given in high volumes, should be used with caution and preferably for short term treatment in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis). Premature and low-birth weight infants may be more likely to develop toxicity. Benzyl alcohol containing products should not be used in pre-term or full-term neonates unless strictly necessary.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. This has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhoea to fatal colitis. *C. difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhoea (CDAD) and is a primary cause of “antibiotic-associated colitis”. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. This form of colitis is characterized by mild, watery diarrhoea that may develop to serious chronic diarrhoea, leukocytosis, fever, serious abdominal cramps that may be accompanied by loss of blood and mucus. Without further treatment peritonitis, shock and toxic megacolon may develop. Antibiotic induced colitis can occur with clindamycin up to 2 to 3 weeks after discontinuation of the treatment. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

It is important to consider the diagnosis of CDAD in patients who present with diarrhoea during or after the administration of antibacterial agents. This may progress to colitis, including pseudomembranous colitis (see section 4.8), which may range from mild to fatal colitis. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including clindamycin, should be discontinued and adequate therapeutic measures should be initiated immediately. 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. Drugs inhibiting peristalsis are contraindicated in this situation. The diagnosis of an antibiotic induced colitis is usually made based on clinical symptoms. The diagnosis can be confirmed by endoscopic demonstration of pseudomembranous colitis or by demonstrating the presence of *Clostridium difficile* and toxins in the faeces.

Medicinal products which discontinue intestinal motility must be avoided.

Clindamycin should be prescribed with caution to individuals with a history of gastro-intestinal conditions, particularly colitis. Antibiotic-induced colitis and diarrhoea

occur more frequently and in more serious forms in debilitated and/or older patients.

Since clindamycin does not diffuse adequately in the cerebrospinal fluid, this drug should not be used to treat meningitis (see section 4.3).

Antagonism between clindamycin and erythromycin was demonstrated *in vitro*. Because of the possible clinical significance, both drugs should not be used simultaneously (see section 4.5).

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

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

Clindamycin phosphate should not be injected intravenously undiluted as a bolus, but should be infused over at least 10-60 minutes (see section 4.2).

Clindamycin appears to have neuromuscular blocking properties that can enhance the effects of other neuromuscular blocking drugs. In patients that are treated with these drugs, clindamycin should, therefore, be used with caution (see section 4.5).

In patients with hypersensitivity, clindamycin phosphate should be administered with caution.

In patients with serious renal and/or serious liver disorders associated to serious metabolic conditions, clindamycin should be administered cautiously. The serum levels of clindamycin should be monitored if high doses are required (see section 4.2).

The hard capsules contain lactose and patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The solution for injection contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Drugs interactions

An antagonism was demonstrated between clindamycin, erythromycin and chemically related macrolides.

Clindamycin administered by injection has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, clindamycin must be used cautiously in patient taking medication such as vecuronium, rocuronium, gentamicin, rapacuronium (with magnesium) or pancuronium. Synergistic effects of other antibiotics together with clindamycin on neuromuscular blocking agents have been described. Careful attention is therefore needed when using antibiotics together

with muscle relaxants, because the synergy effect triggered by the combination could cause deeper muscle relaxation and delay recovery.

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 (such as ritonavir, lopinavir, indinavir, cobicistat, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, grapefruit juice, nefazodone) 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.

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.

4.6 Use in special populations

Pregnancy

There are limited data on the use of clindamycin in pregnant women during the first trimester of pregnancy. Clindamycin crosses the placenta. In clinical trials, the use of clindamycin in pregnant women and the systemic administration of clindamycin during the second and third trimesters, have not been associated with an increased incidence of congenital abnormalities. Animal studies did not reveal any direct or indirect deleterious effects on reproduction (see section 6.1).

The following statement only applies to the *solution for injection*: Benzyl alcohol can cross the placenta (see section 4.4).

As a precautionary measure, it is preferable to avoid the use of clindamycin during the first trimester of pregnancy. The use of clindamycin during the second and third trimester of pregnancy may be considered after establishing the proper diagnosis by the doctor.

Breastfeeding

Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from < 0.5 to 3.8 µg/mL (50 to 100% of the serum level is attained

in the breast milk (see section 5.3)).

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. The developmental and health benefits of breastfeeding for the child 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. If possible clindamycin should not be used during breastfeeding. If a breast-feeding mother needs oral or intravenous clindamycin, it may be considered to temporarily interrupt breastfeeding for the duration of the mother's treatment. If oral clindamycin is used during breastfeeding, the infant should be closely monitored for adverse drug reactions. If these occur, breastfeeding should be discontinued.

Fertility

Fertility studies in rats treated orally with clindamycin revealed no effects on fertility or mating ability (see section 6.1). No data are available on man fertility.

4.7 Effects on ability to drive and use machines

Clindamycin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common ($\geq 1/10$), Common ($\geq 1/100$, $< 1/10$), Uncommon ($\geq 1/1000$, $< 1/100$), Rare ($\geq 1/10000$, $< 1/1000$), Very rare ($< 1/10000$) and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Reactions Table

System Class	Organ	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1000$ to $< 1/100$	Rare $\geq 1/10,000$ to $< 1/1000$	Very Rare $< 1/10,000$	Frequency Not Known (cannot be estimated from available data)
Infestations	and	<i>Pseudomembranous colitis</i> (see section 4.4), <i>Clostridium difficile colitis</i>				<i>Vaginal infection</i>
Blood and lymphatic system disorders		Eosinophilia ^{1,2}				<i>Agranulocytosis, Neutropenia, Thrombocytopenia, Leukopenia</i>
Immune system disorders					<i>Anaphylactic shock</i> [†]	<i>Anaphylactoid reaction, Anaphylactic reaction, Hypersensitivity</i>
Nervous system disorders			Dysgeusia ¹			
Cardiac disorders [†]			Cardio-respiratory arrest ^{†§} ,			
Vascular disorders [†]		Thrombophlebitis ^{††}	Hypotension ^{†§}			
Gastrointestinal disorders		Diarrhoea ⁵ Abdominal pain ²	Vomiting ² , Nausea		Colitis	<i>Oesophageal ulcer</i> *, <i>Oesophagitis</i> *
Hepatobiliary disorders		Liver function test abnormal				<i>Jaundice</i>
Skin and subcutaneous tissue disorders		Rash maculo-papular ⁶	Urticaria, Erythema multiforme ¹ , Pruritus ¹			<i>Toxic epidermal necrolysis (TEN), Steven Johnson syndrome (SJS), Drug reaction with eosinophilia and systemic symptom (DRESS), Acute Generalised Exanthematous Pustulosis (AGEP), Angioedema, Dermatitis exfoliative, Dermatitis bullous, Rash morbilliform</i>

System Class	Organ	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1000$ to $< 1/100$	Rare $\geq 1/10,000$ to $< 1/1000$	Very Rare $< 1/10,000$	Frequency Not Known (cannot be estimated from available data)
General disorders and administration site conditions [†]			Pain [‡] , Injection site abscess [‡]			<i>Injection site irritation[‡]</i>

¹ Frequency for hard capsules: not known.

² Frequency for solution for injection: not known.

³ .

.

⁴ Frequency for solution for injection: uncommon.

⁵ Frequency for hard capsules: uncommon.

[†] Only applicable for solution for injection.

^{*} Only applicable for oral formulations.

[§] Rare instances have been reported following too rapid intravenous administration (see section 4.2).

[‡] These reactions can be reduced to a minimum by deep administration of IM injections and by avoiding prolonged catheterisation in the same vein.

[#] See section 4.4.

If diarrhoea occurs during treatment, the therapy should be discontinued.

In cases of serious anaphylactoid reactions, immediate measures should be taken with the administration of epinephrine (adrenaline), oxygen and intravenous steroids. Mechanical ventilation, possibly with intubation, should also be applied if necessary.

The use of clindamycin phosphate can cause overgrowth of insensitive germs, particularly yeasts.

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.

4.9 Overdose

The toxicity of clindamycin is not linked to the dose. An overdose does not cause specific symptoms. Haemodialysis and peritoneal dialysis are not effective to remove clindamycin from the serum.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Clindamycin binds to the 50S subunit of the bacterial ribosome and inhibits protein synthesis. Clindamycin can be either bactericidal or bacteriostatic, depending on the

sensitivity of the organisms and the concentration of the antibiotic.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic administration - lincosamides
ATC code: J01F F 01

The active substance is clindamycin, a semi-synthetic antibiotic obtained by 7-(S)-chloro-substitution of the 7-(R)-hydroxyl group of lincomycin.

Mechanisms of resistance

Cross resistance between clindamycin and lincomycin is complete. Resistance in staphylococci and streptococci is most often due to methylation of specific nucleotides in the 23S RNA of the 50S ribosomal subunit, which can determine cross resistance to macrolides and streptogramins B (MLS_B phenotype). Macrolide-resistant isolates of these organisms should be tested for inducible resistance to lincomycin/clindamycin using the D-zone test.

Methicilline-sensitive *Staphylococcus aureus* strains are generally sensitive to clindamycin. Clindamycin has a significant activity against many strains of methicilline-resistant staphylococci (MRSA). However, the occurrence of a significant number of clindamycin-resistant MRSA-strains excludes the use of clindamycin for infections due to these organisms without sensitivity tests. *In vitro* some erythromycin-resistant strains of staphylococci rather rapidly develop resistance against clindamycin.

The following germs are usually resistant:

- Aerobic Gram negative bacilli
- *Enterococcus faecalis*
- *Nocardia* species
- *Neisseria meningitidis*
- Strains of *Haemophilus influenzae* (in places where resistance to antibiotics is frequent).

Breakpoints

EUCAST Breakpoints for Clindamycin (from 2014)

Pathogen	Susceptible	Resistant
<i>Staphylococcus</i> spp.	≤ 0.25 mg/l	> 0.5 mg/l
<i>Streptococcus</i> groups A, B, C, G	≤ 0.5 mg/l	> 0.5 mg/l
<i>Streptococcus pneumoniae</i>	≤ 0.5 mg/l	> 0.5 mg/l
Gram-positive anaerobes (excluding <i>Clostridium difficile</i>)	≤ 4 mg/l	> 4 mg/l
Gram-negative anaerobes	≤ 4 mg/l	> 4 mg/l

Prevalence of acquired resistance

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 on 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 lincomycin/clindamycin is recommended.

The following data is available for clindamycin based on European surveillance studies available in 2013.

Commonly susceptible organisms	Remarks
Aerobic gram-positive microorganisms	
<i>Actinomyces israelii</i> ^a	
<i>Staphylococcus aureus</i> (methicillin-susceptible)	
<i>Streptococcus agalactiae</i>	
Viridans group streptococci	
Anaerobic microorganisms	
<i>Bacteroides</i> spp. ^a (excluding <i>B. fragilis</i>)	
<i>Fusobacterium</i> spp. ^a	
<i>Peptococcus</i> spp. ^a	
<i>Prevotella</i> spp.	
<i>Veillonella</i> spp. ^a	
Other microorganisms	
<i>Chlamydia trachomatis</i> ^a	
<i>Chlamydophila pneumoniae</i> ^a	
<i>Gardnerella vaginalis</i> ^a	
<i>Mycoplasma hominis</i> ^a	
Organisms for which acquired resistance may be a problem	Remarks
Aerobic gram-positive microorganisms	
<i>Staphylococcus aureus</i> (methicillin-resistant) ^b	
<i>Staphylococcus epidermidis</i> ^b	
<i>Staphylococcus haemolyticus</i>	
<i>Staphylococcus hominis</i>	
<i>Streptococcus pneumoniae</i>	Resistance rates between > 20 and 49% in some European countries
Aerobic gram-negative microorganisms	
<i>Moraxella catarrhalis</i> ^c	
Anaerobic microorganisms	
<i>Bacteroides fragilis</i>	
<i>Clostridium perfringens</i>	Higher resistance rates in Spain (10-20%)
<i>Peptostreptococcus</i> spp.	Higher resistance rates in Spain (10-20%)

<i>Propionibacterium</i> spp.	
Inherently resistant organisms	
Aerobic gram-positive microorganisms	
<i>Enterococcus</i> spp.	
<i>Listeria monocytogenes</i>	
Aerobic gram-negative microorganisms	
<i>Escherichia coli</i>	
<i>Klebsiella</i> spp.	
<i>Neisseria gonorrhoeae</i>	
<i>Pseudomonas aeruginosa</i>	
Anaerobic microorganisms	
<i>Clostridium difficile</i>	
Other microorganisms	
<i>Mycoplasma pneumoniae</i>	
<i>Ureaplasma urealyticum</i>	

^aUpdated information not available.

^bAt least one European region has reported resistance rates higher than 50%.

^cMost isolates have inherently intermediate resistance.

Antagonism was demonstrated between clindamycin and erythromycin and chemically related macrolides. Clindamycin does not demonstrate any antagonism with penicillins.

Although clindamycin hydrochloride is active both *in vivo* and *in vitro*, clindamycin phosphate are not active *in vitro*. However, both compounds are *in vivo* rapidly hydrolysed to the active base.

5.3 Pharmacokinetic properties

Absorption

After oral administration clindamycin is rapidly and nearly completely (90%) absorbed. The following table gives the mean plasma levels after oral administration of 150 mg in adults.

Way of administration and posology	Time/plasma levels in µg/ml				
	45 min	1 hr.	2 hr.	3 hr.	6 hr.
Oral, 150 mg HCl	2.5	2.48	1.88	1.51	0.7

1 to 3 hours following intramuscular injection of 600 mg of clindamycin phosphate, serum peak levels of clindamycin of 9 µg/ml were observed. Following intravenous infusion of 300 mg in 10 min and 600 mg in 20 min, respectively, serum peak levels of 7 µg/ml and 10 µg/ml, respectively, are reached at the end of the infusion.

Table 1 gives the mean serum levels after the administration of clindamycin phosphate. Clindamycin serum levels can be maintained above the *in vitro* MIC's for most sensitive organisms by administering clindamycin phosphate every 8 to 12 hours in adults or every 6 to 8 hours in children by continuous I.V. infusion. Steady state levels are reached after the third dose.

Table 1

Dose	Clindamycin µg/ml	Clindamycin phosphate µg/ml
<u>Adults (after the steady state)</u>		
300 mg I.V. in 10 min every 8 u.	7	15
600 mg I.V. in 20 min every 8 u.	10	23
600 mg I.V. in 30 min every 6 u.	10.9	
600 mg I.V. in 30 min every 8 u.	10.8	
900 mg I.V. in 30 min every 8 u.	14.1	
900 mg I.V. in 30 min every 12 u.	11	29
1200 mg I.V. in 45 min every 12 u.	14	49
300 mg I.M. every 8 u.	6	3
600 mg I.M. every 12 u.	9	3

Dose	Clindamycin µg/ml
<u>Children (first dose) ⁽¹⁾</u>	
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⁾ Patients in this group were treated for existing infections.

Distribution

The protein binding is between 40% and 90% of the administered dose. No accumulation could be demonstrated with oral administration.

Clindamycin easily penetrates in most body fluids and tissues. In bone tissue a level of approx. 40% (20%-75%) of the serum level is reached, in the mother's milk 50%-100%, in synovial fluid 50%, in the sputum 30%-75%, in the peritoneal fluid 50%, in foetal blood 40%, in pus 30%, in pleural fluid 50%-90%. Clindamycin does not penetrate, however, in the cerebrospinal fluid, not even in the event of meningitis.

Biotransformation

Clindamycin has a half-life of approx. 1 1/2 - 3 1/2 hours. This is somewhat longer in patients with a significantly reduced function of the liver or of the kidneys. The dose regimen should, however, not be adjusted in cases of moderately seriously reduced

function of the kidneys or of the liver.

Clindamycin is relatively extensively metabolised.

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.

Excretion

The excretion in the urine is 10%-20% and in the faeces some 4% in microbiologically active form. The remainder is excreted as biologically inactive metabolites. The excretion is mainly via the bile and the faeces.

6 NON CLINICAL PROPERTIES

6.1 Animal Toxicology and Pharmacology

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

7. DESCRIPTION

Capsules –

150 mg Capsules - Hard opaque gelatin capsules, size N° 1, with white cap and body, overprinted in black with Pfizer logo and the code “CLIN 150” and containing a white powder.

300 mg Capsules - Hard opaque gelatin capsules, size N° 0, with white cap and body, overprinted in black with Pfizer logo and the code "CLIN 300" and containing a white powder.

Injection –

The finished product is a sterile solution, which contains 150 mg/mL of clindamycin phosphate.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Capsules (150 mg/300 mg):

None specific

Injection (300 mg/600 mg):

Solutions of clindamycin salts have an acidic pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Incompatibility has been reported with aminophylline, ampicillin sodium, barbiturates, calcium gluconate, ceftriaxone sodium, idarubicin hydrochloride, magnesium sulphate, phenytoin sodium and ranitidine hydrochloride.

It may be incompatible with tobramycin sulphate under certain circumstances: admixtures in syringe, and solutions in glucose injection, have been reported to be unstable.

COMPATIBILITIES:

Solutions of clindamycin phosphate in 5% dextrose in water and in sodium chloride solutions, to which one of the following antibiotics are added in the usual concentration remain stable for at least 24 hours: amikacin sulphate, aztreonam, cefamandole nafate, cefazolin sodium, cefotaxime sodium, ceftazidime sodium, ceftizoxime sodium, gentamicin sulphate, netilmicin sulphate, piperacillin and tobramycin.

The compatibility and the stability of these mixtures can vary depending on the concentration and other conditions.

8.2 Shelf-life

Capsules (150 mg/300 mg):

60 months

Injection (300 mg/600 mg):

24 months

8.3 Packaging information

Capsules (150 mg/300 mg):

Carton containing 2 blister strips, each blister strip containing 10 capsules.

Injection 300 mg:

Carton containing ampoule pack of 2 ml.

Injection 600 mg:

Carton containing ampoule pack of 4 ml.

8.4 Storage and handling instructions

Capsules

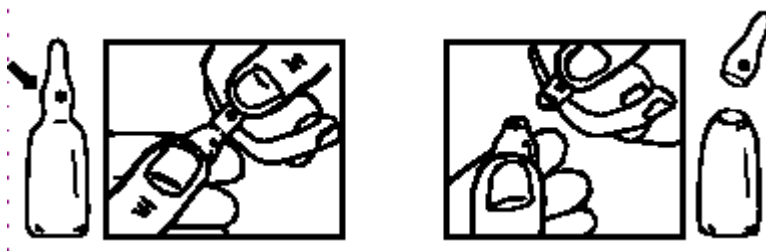
Store below 30°C.

Injection

Store at 2°C to 8°C.

INDICATIONS FOR OPENING THE AMPOULE

Exert pressure on the ampoule with the point towards you, as indicated on the graph.



Additional comments on carton:

Keep out of reach of children.

If given intravenously, must be diluted before use.

9. PATIENT COUNSELING INFORMATION

Patients should be counseled that antibacterial drugs, including Clindamycin, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Clindamycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Clindamycin or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late

as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

10. DETAILS OF MANUFACTURER

Capsules –

M/s. Fareva Amboise, Zone Industrielle 29 Route Des Industries Poce Sur Cisse (France)
– 37530

Injection – M/s. Pfizer Manufacturing Belgium NV, Rijksweg 12, B-2870 Puurs, Belgium

Imported & Marketed in India by:

Capsules -

M/s. Pfizer Products India Private Limited,
The Capital – B Wing, 1802, 18th Floor,
Plot No. C-70, G Block, Bandra Kurla Complex,
Bandra (E), Mumbai – 400 051, India

Injection –

M/s. Pfizer Products India Private Limited,
The Capital – B Wing, 1802, 18th Floor,
Plot No. C-70, G Block, Bandra Kurla Complex,
Bandra (E), Mumbai – 400 051, India

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Capsules – Import License no. FF-307-30369

Injection – Import License no. FF-362-12005

12. DATE OF REVISION

September 2021