DALACIN C

150 mg Hard Capsules
300 mg Hard Capsules

Clindamycine hydrochloride

Reference market: France

AfME markets using same LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

WARNING

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin HCl 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.

Because clindamycin HCl therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate, as described in the INDICATIONS AND USAGE section. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with 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.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

1. NAME OF THE MEDICINAL PRODUCT

DALACIN C 150 mg, capsules
DALACIN C 300 mg, capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For one 150 mg Capsule:

Clindamycin base ..... 150.00 mg
Quantity corresponding to Clindamycin hydrochloride, hydrated

For one 300 mg Capsule:

Clindamycin base ..... 300.00 mg
Quantity corresponding to Clindamycin hydrochloride, hydrated

Excipient with known effect: lactose
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

They derive from the antibacterial and pharmacokinetic characteristics of clindamycin. They are based

on data obtained from clinical studies performed with the medicinal product and its place in the range of currently available antibacterial products.

Treatment of infections:
Clindamycin is indicated for the treatment of severe infections by susceptible micro-organisms causing namely:
- ears, nose and throat infections,
- bronchopulmonary infections,
- stomatological infections,
- skin infections,
- genital infections,
- osteoarticular infections,
- post-surgical abdominal infections,
- septicaemia.

Except for meningeal infections even if caused by susceptible micro-organisms, because the antibiotic does not diffuse into CSF in therapeutically effective quantities.

Prophylaxis:
Prophylaxis of infective endocarditis during dental care and upper respiratory tract procedures performed on an outpatient basis in patients allergic to beta lactams.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology

Treatment of infections:
Adults: 600 to 2,400 mg/24 hours in 2, 3 or 4 doses.
Prophylaxis:
Adults: 600 mg orally in the hour preceding the procedure.
Paediatric population
DALACIN capsules are not suitable for children, who are unable to swallow them whole.
Use of the capsules may not be appropriate to provide the exact doses required in mg/kg to treat children.
Clindamycin posology in children should be adapted based on total body weight, regardless of an obesity.
Treatment of infections:
Children aged over 6 years: 8 to 25 mg/kg/24 hours, in 3 to 4 doses.
Prophylaxis:
Children aged over 6 years: 15 mg/kg orally in the hour preceding the procedure.

Method of administration
Not applicable.

4.3. Contraindications

This medicinal product must never be used:
- in cases of hypersensitivity to the active substance, to lincomycin or to any excipients listed in section 6.1,
- in children aged under 6 years, because of the pharmaceutical form,
- in breast-feeding women (see section 4.6).

4.4. Special warnings and precautions for use

Antibiotic-associated colitis
Pseudomembranous colitis and antibiotic-associated colitis have been observed with use of nearly all antibacterial agents including clindamycin (see section 4.8); they may range in severity from mild to life threatening. Consequently, it is important to consider this diagnosis in the event of diarrhoea occurring during or after the administration of any antibiotic. If an antibiotic-associated colitis arises, clindamycin

must be discontinued immediately; a doctor should be consulted and adequate treatment, including a specific treatment against *Clostridium difficile* should be initiated. Drugs inhibiting peristalsis are contraindicated in this situation.

Hypersensitivity
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 generalised exanthematous pustulosis (AGEP) have been reported in patients receiving clindamycin treatment. In cases of hypersensitivity or severe skin reaction occurs, clindamycin should be discontinued and appropriate medical treatment should be initiated (see sections 4.3 and 4.8).
Clindamycin should be used with caution in patients with a history of asthma or other allergies.
The occurrence early in treatment of generalised erythema with pyrexia and pustules would suggest acute generalised exanthematous pustulosis (see section 4.8); treatment must be discontinued and any further administration of clindamycin is contraindicated.

Hepatic insufficiency
Raised clindamycin serum levels and increased elimination half-life have been reported in cases of hepatic insufficiency.
If therapy is prolonged, liver and kidney functions tests should be performed.

Acute kidney injury
Acute kidney injury, including acute renal failure, has been reported infrequently. In patients receiving prolonged therapy, suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs, monitoring of renal function should be considered (see section 4.8).

Long-term treatment
Long-term treatment should only be undertaken with close monitoring of blood counts, liver enzymes and renal function.
Antibiotic use, particularly for long periods, is associated with the emergence and selection of less susceptible bacteria or the development of fungi. Appropriate treatment must be initiated in the event of superinfection.
This drug must not be used in the treatment of meningitis since clindamycin does not diffuse adequately into cerebrospinal fluid (see section 4.1).

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Combinations requiring precautions for use
+ Vitamin K antagonists:
Increased antivitamin K effect and/or bleeding,
More frequent INR monitoring. If necessary dose adjustment of antivitamin K during treatment with clindamycin and after treatment discontinuation**.**
+ Topical gastrointestinal agents, antacids and adsorbents
Topical gastrointestinal agents, charcoal and antacids (aluminium, calcium and magnesium salts), alone or combined with alginates, reduce the digestive absorption of certain other medicinal products taken simultaneously. Medicinal products for which a reduction in gastrointestinal absorption has been observed include acetylsalicylic acid, H2 blockers and lansoprazole, bisphosphonates, catioresins, certain classes of antibiotics (fluoroquinolones, tetracyclines, lincosamides) and some anti-tubercular agents, digitalis, glucocorticoids, thyroid hormones, phenothiazine neuroleptics, sulpiride, certain beta-blockers, penicillamine, ions (iron, phosphorus, fluorine), chloroquine, ulipristal and fexofenadine.
As a precaution, these topical gastrointestinal agents or antacids should be taken some time apart from any other medicinal product (more than 2 hours, if possible).
+ Ciclosporin
Decrease in the blood concentrations of the immunosuppressive agent, associated with a risk of loss of immunosuppressive activity. Increase monitoring of ciclosporin blood levels and increase its dosage if

required.

+ Cytochrome P450 (CYP) 3A4 inducers

Clindamycin is mainly metabolised by CYP3A4, and to a lesser extent by CYP3A5, to form the major metabolite, clindamycin sulphoxide, and the minor metabolite, N-desmethylclindamycin. Therefore, CYP3A4 and CYP3A5 inhibitors may reduce clindamycin clearance, and the inducers of these isoenzymes may increase clindamycin clearance. In the presence of potent CYP3A4 inducers such as rifampicin, monitoring of loss of efficacy is required.

In vitro studies indicate that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6, and only moderately inhibits CYP3A4. Therefore, clinically significant interactions between clindamycin and coadministered medicinal products metabolised by these cytochromes are unlikely.

+ Tacrolimus

Decrease in the blood concentrations of the immunosuppressive agent, associated with a risk of loss of immunosuppressive activity. Increase monitoring of tacrolimus blood levels and increase its dosage if required.

Specific problems related to changes in the INR

Several cases of increases in the activity of antivitamin K have been reported in patients receiving antibiotics. Risk factors include the degree of severity of infection or inflammation and the patient's age and general condition. In such cases, it is difficult to discern whether the infection or the treatment is responsible for the change in INR. However, certain classes of antibiotics are more implicated than others, namely fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

4.6. Fertility, pregnancy and lactation

Pregnancy

In embryo foetal development studies (see section 5.3) no toxicity was observed on the development except at doses that caused toxicity in the mother.

Clindamycin crosses the placenta.

Exposure data of clindamycin by systematic or topical route in pregnant woman during the first trimester are limited.

Available data of exposure during the second and third trimesters, are numerous and an increased foetal risk has not been reported.

Thus, taken into account the available data, it is preferable as a precaution not to use clindamycin during the first trimester of pregnancy.

During the second and third trimesters of pregnancy, clindamycin can be used if necessary.

Breast-feeding

The excretion of clindamycin in human breast milk is low and the quantities ingested are much lower than paediatric therapeutic doses after systemic use.

Therefore, breast-feeding is possible whilst taking this antibiotic. However, in cases of diarrhoea, blood in stools, candidiasis or cutaneous rash in the infant, the continuation of breast-feeding (or off taking the medicine) must be reviewed.

Fertility

Fertility studies in rats treated with clindamycin revealed no effects on fertility or mating ability.

4.7. Effects on ability to drive and use machines

DALACIN 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.

Following the organ classification system, the adverse reactions are listed below in order of decreasing frequency and then of clinical severity using the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Frequency not known (cannot be estimated from the available data).

System Organ Class	Common ≥ 1/100 to <1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1 000	Very Rare < 1/10,000	Frequency not Known (cannot be estimated from the available data)
Infections and infestations	Pseudomembranous colitis*#				*Clostridium difficile colitis*#, Vaginal infection#
Blood and Lymphatic System Disorders					Agranulocytosis#, Neutropenia#, Thrombocytopenia*, Leukopenia#, Eosinophilia, Thrombocytopenic purpura
Immune System Disorders					Anaphylactic shock#, Anaphylactic reaction#, Hypersensitivity reactions such as Quincke's oedema and anaphylaxis in some patients allergic to penicillin#
Nervous System Disorders					Dysgeusia
Gastrointestinal disorders	Diarrhoea, Adbominal pain	Vomiting, Nausea			Oesophageal ulcer#, Oesophagitis#
Hepatobiliary Disorders					Jaundice#
Skin and Subcutaneous Tissue Disorders		Maculo-papular rash Urticaria			Toxic epidermal necrolysis (Lyell syndrome)#, Stevens-Johnson syndrome (SJS)#, DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome#, Acute generalised exanthematous pustulosis (AGEP)#, Angio-oedema#, Exfoliative dermatitis#, Bullous dermatosis#, Erythema multiforme, Pruritus, Morbilliform rash #
Renal and urinary disorders					Acute kidney injury*
Musculoskeletal					Cases of polyarthritis have been reported.
Investigations	Liver function test abnormal				

* see section 4.4
# post-marketing data

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing 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 according to their local country requirements.

To Report side effects

- **Saudi Arabia:**

National Pharmacovigilance Center (NPC) Call center: 19999 E-mail: npc.drug@sfda.gov.sa Website :https://ade.sfda.gov.sa/

- **Other GCC States**

- *Please contact the relevant competent authority.*

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: lincosamides, ATC code: J01FF01.
Clindamycin is an antibiotic from the lincosamide family.

Mechanism of action
Clindamycin inhibits the synthesis of bacterial proteins by bonding to the 50S sub-unit of the bacterial ribosome. At normal doses, clindamycin has a bacteriostatic activity *in vitro*.

Pharmacokinetic-pharmacodynamic relationship
The percentage of time during which the concentration of the antibiotic is above the minimum inhibitory concentration (MIC) of the bacteria between two administrations (%T>MIC) is the most predictive parameter for the efficacy of clindamycin.

Resistance
Clindamycin resistance is most often caused by mutations of the site where the antibiotic bonds to the rRNA or methylation of 23S RNA specific nucleotides of the 50S ribosome sub-unit. These changes can determine *in vitro* cross-resistance to macrolides and B streptogramins (MLS_B phenotype).
Resistance mechanisms can also be due to active efflux.
Clindamycin resistance can be induced by macrolides in macrolide-resistant bacteria strains.
Full cross-resistance between clindamycin and lincomycin is possible.
The incidence of clindamycin resistance is higher among methicillin-resistant staphylococcus strains and penicillin-resistant pneumococcal strains.

Critical concentrations
According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), critical concentrations for clindamycin that separate susceptible strains (S) from resistant strains (R) are as follows:

	Critical concentrations of MIC (mg/L)	
Pathogen	**Susceptible**	**Resistant**

Staphylococcus spp.	S ≤ 0.25 mg/L	R > 0.5 mg/L
Streptococcus Groups A, B, C and G	S ≤ 0.5 mg/L	R > 0.5 mg/L
Streptococcus pneumoniae	S ≤ 0.5 mg/L	R > 0.5 mg/L
Streptococci from *Viridans* group	S ≤ 0.5 mg/L	R > 0.5 mg/L
Gram-positive anaerobes apart from *Clostridium difficile*	S ≤ 4 mg/L	R > 4 mg/L
Gram-negative anaerobes	S ≤ 4 mg/L	R > 4 mg/L
Corynebacterium spp.	S ≤ 0.5 mg/L	R > 0.5 mg/L

Antibacterial spectrum of activity

The prevalence of acquired resistance may vary geographically and with time for certain species. Therefore, local information on the prevalence of resistance is useful, particularly for severe infections. If required, it is desirable to have a specialist opinion, mainly when the benefit of some medicinal products for certain infections can be questioned due to the level of prevalence of local resistance.

Classes
NORMALLY SUSCEPTIBLE SPECIES **Gram-positive aerobes** *Bacillus cereus* *Corynebacterium diphtheriae* Methicillin-susceptible *Staphylococcus* *Streptococcus agalactiae* **Gram-negative aerobes** *Campylobacter* **Anaerobes** *Actinomyces* *Capnocytophaga* *Clostridium perfringens* *Eubacterium* *Fusobacterium* *Gardnerella vaginalis* *Porphyromonas* *Prevotella* *Propionibacterium acnes* *Veillonella* **Other** *Chlamydia trachomatis* Leptospires *Mycoplasma hominis* *Mycoplasma pneumoniae*
VARIABLY SUSCEPTIBLE SPECIES **(≥ 10% acquired resistance)** **Gram-positive aerobes** *Enterococcus faecium* *Erysipelothrix* Methicillin-resistant *Staphylococcus*

Streptococcus pneumoniae *Streptococcus pyogenes* Oral Streptococci **Anaerobes** *Bacteroides* *Clostridium* (other than *difficile* and *perfringens*) *Mobiluncus* *Peptococcus* *Peptostreptococcus* *Propionibacterium acnes*
NATURALLY RESISTANT SPECIES **Gram-positive aerobes** *Corynebacterium jeikeium* *Enterococcus* spp. (other than *Enterococcus faecium*) *Listeria* *Nocardia asteroides* *Rhodococcus equi* **Gram-negative aerobes** Non fermenting gram-negative bacilli *(Acinetobacter, Pseudomonas, etc.)* Enterobacteria *Haemophilus* *Legionella* *Branhamella catarrhalis* *Neisseria* *Pasteurella* **Anaerobes** *Clostridium difficile* **Other** Mycobacteria *Ureaplasma urealyticum*

Anti-parasitic activity
Clindamycin shows *in vitro* and *in vivo* activity against *Toxoplasma gondii*.

5.2. Pharmacokinetic properties

Absorption
Following oral administration, clindamycin is rapidly and almost completely absorbed (90% of the ingested dose).
Simultaneous intake of food has practically no effect on plasma concentrations

Distribution

- *Serum concentrations*: in healthy adults, peak plasma concentrations of about 2 - 3 mg/L are observed one hour after oral administration of 150 mg of clindamycin hydrochloride, and 4 - 5 mg/L following oral administration of 300 mg. Plasma concentrations then decrease slowly but remain above 1 mg/L for more than 6 hours.
  Plasma concentrations increase linearly with the dose taken.
  Serum concentrations have been reported to be slightly lower in diabetic patients compared to healthy subjects.
  The mean serum biological half-life of clindamycin is 2.5 hours.
- *Plasma protein binding*
  Plasma protein binding is substantial: between 80 and 94%.
- *Tissue and humoral circulation*
  Clindamycin is widely distributed at very high concentrations in extra- and intra-cellular fluids and in tissues.
  Diffusion into CSF is very limited.

Biotransformation
Clindamycin undergoes hepatic metabolism.
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.

Elimination
About 10% of a dose is excreted in the urine as active drug and about 3.6% in the faeces; the remainder is excreted as inactive metabolites.
Clindamycin serum concentrations are not changed by haemodialysis or peritoneal dialysis.
Obese Patients
An analysis of pharmacokinetic data in obese and non obese pediatric patients aged 2 to less than 18 years and obese and non obese adults aged 18 to 20 years, shown based on a pharmacokinetic model that clindamycin clearance and volume of distribution normalized by total body weight are comparable regardless of obesity.

5.3. Preclinical safety data
In oral embryo foetal development studies in rats and in subcutaneous embryo foetal development studies in rats and rabbits, no developmental toxicity was observed except at doses that produced maternal toxicity.
Genotoxicity studies haven't shown a genotoxic activity. No cancerogenesis studies have been conducted with clindamycin.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Maize Starch, Talc, Magnesium Stearate, and Lactose Monohydrate.

6.2. Incompatibilities

Clindamycin is physicochemically incompatible with the following medicinal products: ampicillin, phenytoin, barbiturates, aminophylline, calcium gluconate, magnesium sulphate.

6.3. Shelf life

36 Months
Do not use Dalacin C 150 & 300 mg after the expiry date which is stated on the card packaging or carton. The expiry date refers to the last day of that month.

6.4. Special precautions for storage

Keep this medicine out of the sight and reach of children.
Store below 25°C.

6.5. Nature and contents of container

Dalacin C 150mg: 16 capsules in heat-formed blister packs (Aluminium foil/PVC).
Dalacin C 300mg: 16 capsules in heat-formed blister packs (Aluminium foil/PVC).

6.6. Special precautions for disposal and other handling

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

7. MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder
Pfizer Holding France
23-25 Avenue Docteur Lannelongue
75014 Paris
France

MANUFACUTRED BY
Fareva Amboise
Zone Industrielle
29 route des Industries
37530 Pocé-sur-Cisse
France

8. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 01 January 1983.
Date of latest renewal: 17 September 2023

9. DATE OF REVISION OF THE TEXT

January 2023