Dalacin C®

150 mg Hard Capsules

300 mg Hard Capsules

Clindamycin HCl

Reference market : France

SUMMARY OF PRODUCT CHARACTERISTICS

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 form

For one capsule.

For one capsule one 300 mg Capsule:
Clindamycin base ..... 300.00 mg

Quantity corresponding to Clindamycin hydrochloride, hydrated form

For one capsule.

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 C 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.

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 breastfeeding 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,

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 41).

Lactose

This medicinal product contains lactose. Its use should be avoided in patients presenting with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases).

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

Clindamycin is excreted in low concentration in human breast milk. A risk of gastrointestinal

disorders exists in nursing infants. Therefore, as a precautionary measure, breastfeeding should be avoided during the time of their treatment.

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	**Very Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1000**	**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

System Organ Class	Very Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000	Very Rare < 1/10,000	Frequency not Known (cannot be estimated from the available data)
					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 [#]
Investigations	Liver function test abnormal				

* see section 4.4
[#] post-marketing data

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 according to their local country requirements.

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.

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

For Dalacin C 150mg Capsules:
Maize starch, talc, magnesium stearate, lactose.

Composition of the capsule shell: gelatin, titanium dioxide.

For Dalacin C 300mg Capsules:

Maize starch, talc, magnesium stearate, lactose.

Composition of the capsule shell (lavender colour): indigo carmine, erythrosine, titanium dioxide, gelatin.

6.2. Incompatibilities

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

6.3. Shelf life

Do not use Dalacin C 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

Do not store above 25°C.

6.5. Nature and contents of container

Dalacin C 150mg: 12, 16 or 100 capsules in heat-formed blister packs (Aluminium foil/PVC).

12 capsules in heat-formed blister packs (Aluminium foil/PVC) pre-cut (unit dose blisters).

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

16 capsules in heat-formed blister packs (Aluminium foil/PVC) pre-cut (unit dose blisters).

Not all pack sizes or strengths may be marketed.

6.6. Special precautions for disposal and other handling

Keep out of sight and reach of children.

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. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

PFIZER HOLDING FRANCE
23-25 AVENUE DU DOCTEUR LANNELONGUE
75014 PARIS
FRANCE

MANUFACUTRED BY

FAREVA AMBOISE
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29 ROUTE DES INDUSTRIES
37530 POCE-SUR-CISSE
France

8. DATE OF REVISION OF THE TEXT

April 2019.

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists