1. NAME OF THE MEDICINAL PRODUCT

Clindamycin Orifarm 300 mg capsules, hard.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:
clindamycin hydrochloride equivalent to 300 mg clindamycin.

Excipient with known effect:
283 mg lactose/ Clindamycin 300 mg capsules

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.
Clindamycin capsules are white/white hard capsules with a marking of 'CLIN 300' on the capsule body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clindamycin is indicated for the treatment of:
Serious infections caused by anaerobic bacteria, including intra-abdominal infections, skin and soft tissue infections. As needed, clindamycin should be administered in conjunction with another antibacterial agent that is active against gram negative aerobic bacteria.
- Tonsillitis
- Dental infection

Consideration should be given to the official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults
The usual dose is 150-450 mg every six hours, depending on the severity of the infection.

Elderly patients
Dosage requirements in elderly patients should not be influenced by age alone.

Paediatric population
The usual dose is 3-6 mg/kg every six hours depending on the severity of the infection (not to exceed the adult dose).

Clindamycin capsules are not suitable for children who cannot swallow the capsules whole or when an appropriate dosage is not possible with the available strengths. It may be necessary to use an alternative formulation in some cases.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate impairment of renal function. In patients with severe renal impairment or anuria, plasma concentration should be monitored. Depending on the results, this measure can make a reduction in dosage or an increase in the dose interval of 8 or even 12 hours necessary**.**

Hepatic impairment
In patients with moderate to severe hepatic impairment, elimination half-life of clindamycin is prolonged. A reduction in dosage is generally not necessary if clindamycin is administered every 8 hours. However, the plasma concentration of clindamycin should be monitored in patients with severe hepatic impairment. Depending on the results, this measure can make a reduction in dosage or an increase in the dose intervals necessary.

Method of administration
<{(Invented) name}> is given orally. Clindamycin capsules should always be swallowed whole with a full glass of water whilst in an upright position (i.e. sitting or standing). The capsules must not be opened due to the risk of oesophageal injury.
Absorption of Clindamycin capsules is not appreciably modified by the presence of food.

4.3 Contraindications

Hypersensitivity to the active substance, lincomycin or to any of the excipients listed in section 6.1

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).

Clindamycin should only be used in the treatment of serious infections. In considering the use of the product, the practitioner should bear in mind the type of infection and the potential hazard of the diarrhoea which may develop, since cases of colitis have been reported during, or even two or three weeks following, the administration of clindamycin.

Studies indicate a toxin(s) produced by clostridia (especially Clostridium difficile) is the principal direct cause of antibiotic-associated colitis. These studies also indicate that this toxigenic

clostridium is usually sensitive in vitro to vancomycin. When 125 mg to 500 mg of vancomycin are administered orally four times a day for 7 - 10 days, there is a rapid observed disappearance of the toxin from faecal samples and a coincident clinical recovery from the diarrhoea. (Where the patient is receiving cholestyramine in addition to vancomycin, consideration should be given to separating the times of administration).

Colitis is a disease which has a clinical spectrum from mild, watery diarrhoea to severe, persistent diarrhoea, leucocytosis, fever, severe abdominal cramps, which may be associated with the passage of blood and mucous. If allowed to progress, it may produce peritonitis, shock and toxic megacolon. This may be fatal.

The appearance of marked diarrhoea should be regarded as an indication that the product should be discontinued immediately. The disease is likely to follow a more severe course in older patients or patients who are debilitated. Diagnosis is usually made by the recognition of the clinical symptoms, but can be substantiated by endoscopic demonstration of pseudomembranous colitis. The presence of the disease may be further confirmed by culture of the stool for Clostridium difficile on selective media and assay of the stool specimen for the toxin(s) of C. difficile.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhoea 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Precautions: Caution should be used when prescribing clindamycin to individuals with a history of gastro-intestinal disease, especially colitis.

Since clindamycin does not diffuse adequately into cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

Laboratory tests for renal and hepatic function should be carried out during prolonged therapy. Close monitoring is also recommended in patients with renal or hepatic insufficiency and in neonates and infants, all of whom may require dose reduction and/or an extended interval between doses.

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

Prolonged administration of clindamycin, as with any anti-infective, may result in super – infection due to organisms resistant to clindamycin.

Care should be observed in the use of clindamycin in atopic individuals.

<{(Invented) name}> contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The choice of clindamycin should be based on factors such as severity of the infection, the prevalence of resistance to other suitable agents and the risk of selecting clindamycin-resistant bacteria.

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. It should be used with caution, therefore, in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because of possible clinical significance the two drugs should not be administered concurrently.

Clindamycin is metabolized predominantly by CYP3A4, and to a lesser extent by CYP3A5, to the major metabolite clindamycin sulfoxide and minor metabolite N-desmethyl clindamycin. Therefore, inhibitors of CYP3A4 and CYP3A5 may increase clindamycin plasma concentrations. Some examples of strong CYP3A inhibitors are itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir and cobicistat. Caution should be exercised if clindamycin is used in combination with strong CYP3A4 inhibitors. Inducers of these enzymes may increase the clearance of clindamycin, resulting in decreased plasma concentrations. In a prospective study with orally administered clindamycin, approximately 80% lower trough levels of clindamycin were seen if co-administered with rifampicin, a strong inducer of CYP3A4. In the presence of strong CYP3A4 inducers such as rifampicin, St. John's wort (*Hypericum perforatum*), carbamazepine, phenytoin and phenobarbital, patients should be monitored in relation to impaired effect of treatment.

In vitro studies indicate that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6. Therefore, some clinically significant effects of clindamycin on concomitantly administered drugs metabolized by these CYP enzymes are unlikely. Based on *in vitro* data, oral administration of clindamycin may inhibit intestinal CYP3A4. Thus, the exposure of orally administered CYP3A4 substrates, e.g., dihydroergotamine, ergotamine, ergometrine, midazolam, triazolam, amiodarone, quinidine, cisapride, pimozide, alfuzosin, simvastatin, lovastatin, and sildenafil, may be increased if co-administered with orally administered clindamycin. Caution should be exercised if oral clindamycin is used in combination with orally administered CYP3A4 substrates, especially those with narrow therapeutic windows.

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 Fertility, pregnancy and lactation

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

In clinical trials with pregnant women, the systemic administration of clindamycin during the second and third trimesters has not been associated with an increased frequency of congenital abnormalities. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

Clindamycin should be used in pregnancy only if clearly needed.

Oral and subcutaneous reproductive toxicity studies in rats and rabbits revealed no evidence of impaired fertility or harm to the foetus due to clindamycin, except at doses that caused maternal toxicity. Animal reproduction studies are not always predictive of human response.

Breast-feeding
Clindamycin is excreted in breast milk. Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from 0.5 to 3.8 μg/ml. As clindamycin can cause serious adverse effects on the intestinal flora in nursing infants such as diarrhea or skin rashes, it is not recommended to use systematically administered clindamycin during breast-feeding and a decision should be made whether to discontinue breast-feeding or to select an alternative treatment option. Developmental and health benefits from breast-feeding should be considered together with the mother's clinical need for clindamycin.

Fertility
In animal studies, clindamycin had no effect on fertility or mating ability (see section 5.3).

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. The frequency grouping is defined 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 Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Common**	**Uncommon**	**Not Known**
Infections and Infestations	pseudomembranous colitis*#		*clostridium difficile* colitis*#, vaginal infection*
Blood and			agranulocytosis*,

Lymphatic System Disorders			neutropenia*, thrombocytopenia*, leukopenia*, eosinophilia
Immune System Disorders			anaphylactic shock*, anaphylactoid reaction*, anaphylactic reaction*, hypersensitivity*
Nervous System Disorders			dysgeusia
Gastrointestinal Disorders	diarrhoea, abdominal pain	vomiting, nausea	oesophageal ulcer*, oesophagitis*
Hepatobiliary Disorders			jaundice*
Renal and urinary disorders			acute kidney injury#
Skin and Subcutaneous Tissue Disorders		rash maculopapular, urticaria	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*, erythema multiforme*, pruritus, rash morbilliform*
Investigations	Liver function test abnormal		

* ADR identified post-marketing.
# See section 4.4.

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 via the national reporting system listed in Appendix V

4.9 Overdose

The serum biological half-life of clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by haemodialysis or peritoneal dialysis.

If an allergic adverse reaction occurs, therapy should be with the usual emergency treatments, including corticosteroids, adrenaline and antihistamines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lincosamides

ATC classification: J01FF01

Mechanism of action
Clindamycin is a lincosamide antibiotic which inhibits bacterial protein synthesis. It binds to the 50S subunit of the bacterial ribosome and affects both the formation of the ribosome and the translation process.. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains. Clindamycin hydrochloride is active both *in vitro* and *in vivo*. Clindamycin phosphate and clindamycin palmitate are inactive *in vitro,* but are rapidly hydrolysed *in vivo* to the active base.

Pharmacodynamic properties
The effect is dependent on the time that the active substance exceeds the minimum inhibitory concentration (MIC) of the pathogen (%T>MIC).

Mechanism of resistance
Resistance to clindamycin usually occurs due to mutations at the rRNA binding sites for antibiotics or due to methylation of specific nucleotides in the 23S RNA on the 50S subunit of the ribosomes. These changes may determine *in vitro* cross-resistance to macrolides and streptogramin B (MLS_B phenotype). Sometimes resistance is due to changes in the ribosomal proteins. Resistance to clindamycin may be inducible by macrolides in macrolide resistant bacterial isolates. Inducible resistance can be proven by a disk test (D-zone test) or in broth. Less common resistance mechanisms are antibiotic modification and active efflux. There is complete cross-resistance between clindamycin and linkomycin. As with many types of antibiotics, the incidence of resistance varies with bacterial species and geographical area. The incidence of resistance to clindamycin is higher among methicillin-resistant staphylococcal isolates and penicillin-resistant pneumococcal isolates than among organisms sensitive to such agents.

Susceptibility
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 local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Especially

in case of severe infections or treatment failure it is recommended to carry out a microbiological diagnosis including a verification of the pathogen and its sensitivity to clindamycin.

Species
Susceptible **Gram-positive aerobes** *Staphylococcus aureus** *Staphylococcus epidermidis* *Streptococcus pneumonia* *Streptococcus pyogenes* *Streptococcus viridans* **Anaerobes** *Bacteriodes fragilis* group *Bacteroides melaninogenicus* *Bifidobacterium* spp. *Clostridium perfringens* *Eubacterium* spp *Fusobacterium* spp. *Peptococcus* spp. *Peptostreptococcus* spp. *Propionibacterium* spp. *Veillonella* spp.
Resistant *Clostridia* spp. *Enterococci* *Enterobacteriaceae*

*Up to 50% of methicillin-susceptible *S. aureus* have been reported to be resistant to clindamycin in some areas. More than 90% of methicillin-resistant *S.aureus* (MRSA) are resistant to clindamycin and it should not be used while awaiting susceptibility test results if there is any suspicion of MRSA.

Breakpoints

Resistance is most commonly defined as concentration for susceptibility (breakpoints) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for systemically administered antibiotics.

Breakpoints from EUCAST are listed below.

	MIC breakpoints (mg/l)		**Breakpoint for zone diameter (mm)** [a]	
Organism	**S≤**	**R>**	**S≥**	**R<**
Staphylococcus spp.	0.25	0.5	22	19
Streptococcus	0.5	0.5	17	17

group A, B, C and G				
Streptococcus pneumoniae	0.5	0.5	19	19
Streptococci viridans	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 microgram of clindamycin
NA = not relevant; S = sensitive; R = resistant

5.2 Pharmacokinetic properties

Absorption
After oral administration clindamycin is absorbed quickly and almost completely (>90%). The absorption is not affected by food. The peak plasma concentration is achieved within approximately 45 minutes after oral administration. The bioavailability is non-linear and decreases with increasing doses. Following a 600 mg dose the absolute bioavailability is 53±14%.

Distribution
Clindamycin is widely distributed in body fluids and tissues. It diffuses across the placenta but not the healthy blood-brain barrier. 68 – 93 % of clindamycin in the circulation is bound to plasma proteins. Clindamycin is distributed very highly intracellular due to the lipophilic properties. The intracellular concentrations are 10-50 times higher than the extracellular concentrations.

Biotransformation
The majority of clindamycin undergoes metabolism. *In vitro* studies suggests that clindamycin is metabolized by CYP3A4 and to a lesser extent CYP3A5, whereby clindamycin sulphoxide and the minor metabolite N-desmethyl clindamycin are formed.

Elimination
Half-life is approximately two and a half hour in children and approximately 3 hours in adults. Clindamycin is excreted as biological active and biological inactive metabolites in faeces, urine and bile. Faecal excretion is predominant. About 10% of the drug is excreted in the urine as active drug and about 4% in the faeces; the remainder is excreted as inactive metabolites.

Characteristics in patients

Elderly:
The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate are not altered by increased age.

Patients with renal impairment:

In the presence of renal impairment, elimination half-life is prolonged; however, a dosage reduction is unnecessary in the event of mild to moderate impairment of renal function.

Patients with hepatic impairment:
In patients with moderate to severe hepatic impairment the half life is prolonged, but when giving the dose every 8 hours, accumulation is rarely seen. Dose reduction is normally not necessary in patients with hepatic impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of repeat dose toxicity, reproductive toxicity or genotoxicity. Carcinogenicity studies have not been conducted.
In dogs, repeated high oral doses produced ulceration of the mucosa of the stomach and gall bladder.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Talc
Magnesium Stearate

Capsule shell
Gelatin
Titanium dioxide (E 171)

Printing ink
Shellac
Iron oxide black (E172)
Propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

The blister pack (PVC/aluminium) contains 20, 24, 28, 30, 32 or 100 capsules, respectively. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be complete nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2025-05-13