Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dalacin C 150 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 150 mg of clindamycin base.

Excipient(s) with known effect:
Lactose monohydrate 210 mg
Medicinal product contains soya oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Capsules.

Size 1, hard opaque gelatin capsules with white body and cap, containing a white powder. The capsule is imprinted with 'CLIN 150' and 'Pfizer'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the treatment of serious infections due to gram-positive organisms, including staphylococci (both penicillinase and non-penicillinase producing), streptococci (except *Streptococcus faecalis*) and pneumococci. It is also indicated in serious infections caused by susceptible anaerobic pathogens.

Clindamycin does not penetrate the blood/brain barrier in therapeutically effective quantities.

4.2 Posology and method of administration

Posology
Adults (including the elderly)
Moderately severe infection: 150 - 300 mg every six hours.
(Note:In cases of beta-haemolytic streptococcal infection, treatment with Dalacin C should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.)

Dosage in elderly
The dosage of clindamycin may require reduction in patients with renal impairment due to prolongation of the serum half-life of this drug. This is particularly important with parenteral dosage.

Paediatric population
Clindamycin should be dosed based on total body weight regardless of obesity. The total daily dose should not exceed the maximum recommended daily dose for adults.

The usual daily dosage is 12 - 24 mg/kg in 4 divided doses.

Dalacin capsules are not suitable for children who are unable to swallow them whole. The use of whole capsules may not be suitable to provide the exact mg/kg doses required for the treatment of children.

Dosage in renal impairment
Clindamycin dosage modification is not necessary in patients with renal insufficiency.

Method of administration

To be taken whole with a full glass of water and no less than 30 minutes before lying down to avoid possible irritation of the oesophagus. Dalacin C hard capsules may be taken without regard to food.

4.3 Contraindications

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

Hypersensitivity to lincomycin.

Hypersensitivity to any soya or peanut products.

Diarrhoea or intestinal inflammatory disease.

4.4 Special warnings and precautions for use

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 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).

Clostridioides Difficile associated diarrhoea
Dalacin C should only be used in the treatment of serious infections. In considering the use of this product the practitioner should bear in mind the type of infection and the potential hazard of the diarrhoea that may develop, since cases of colitis have been reported.
Studies indicate a toxin(s) produced by clostridia (especially *Clostridioides difficile*) is the principal cause of antibiotic-associated colitis. These studies also indicate that this toxigenic *clostridioides* is usually sensitive *in vitro* to vancomycin. When 125-500 mg of vancomycin is administered orally four times a day, there is a rapid observed disappearance of the toxin from faecal samples and a coincident recovery from the diarrhoea.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridioides difficile*. This has been reported with use of nearly all antibacterial agents, including clindamycin. *Clostridioides difficile* produces toxins A and B which contribute to the development of *Clostridioides difficile* associated diarrhoea (CDAD) and is a primary cause of "antibiotic-associated colitis".

It is important to consider the diagnosis of CDAD in patients who present with diarrhoea subsequent to 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. Drugs inhibiting peristalsis are contraindicated in this situation.

Use in patients with atopic syndrome
Care should be observed in the use of Dalacin C in atopic individuals e.g. asthma and allergy.

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

Liver and kidney function tests during prolonged therapy
If therapy is prolonged, liver and kidney function tests and blood counts should be performed. Such monitoring is also recommended in neonates and infants. Safety and appropriate dosage in infants less than one month old have not been established.

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).

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

Prolonged administration of an anti-infective may result in super-infection due to organisms resistant to the anti-infective.

Due to the risk of oesophagitis and oesophageal ulcer, it is important to ensure compliance with administration guidance (see Sections 4.2 and 4.8).

Cross resistance
Attention should also be paid to the possibility of cross resistance between macrolides and lincosamides for some individual bacterial strains (see section 5.1).

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

Clindamycin administered by injection has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore it should be used with caution in patients receiving such agents.

Antibiotics can reduce the efficacy of the oral contraceptive pill. Additional contraceptive precautions should be taken during treatment.

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.

Co-administration of clindamycin with inhibitors of CYP3A4 and CYP3A5
Clindamycin is metabolized predominantly by CYP3A4, and to a lesser extent by CYP3A5, to the major metabolite clindamycin sulfoxide and minor metabolite N-desmethylclindamycin. Therefore, inhibitors of CYP3A4 and CYP3A5 may reduce clindamycin clearance and inducers of these isoenzymes may increase clindamycin clearance. In the presence of strong CYP3A4 inducers such as rifampicin, monitor for loss of effectiveness.

In vitro studies indicate that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6 and only moderately inhibits CYP3A4. Therefore, clinically important interactions between clindamycin and co-administered drugs metabolized by these CYP enzymes are unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

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.

Breast-feeding
Clindamycin is excreted in human milk (see section 5.2) and effects (e.g. diarrhoea, blood in stool and rash) have been shown in breastfed newborns/infants of treated women.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from clindamycin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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

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 ≥ 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**	**Not Known (cannot be estimated from available data)**
Infections and infestations	pseudomembranous colitis[*#]				*Clostridioides difficile* colitis*, vaginal infection*
Blood and Lymphatic System Disorders					agranulocytosis*, 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*
Skin and Subcutaneous Tissue Disorders		rash maculo-papular, 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*, cutaneous vasculitis*, erythema multiforme*, pruritus, rash morbilliform*, symmetrical drug-related intertriginous and flexural exanthema*
Renal and urinary disorders					acute kidney injury[#]

Investigations	Liver function test abnormal				

*ADR identified post-marketing
‡ADRs apply only to oral formulations
≠Possible occurrence of oesophagitis and oesophageal ulcer, particularly if taken in a lying position and/or with a small amount of water.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

In cases of overdosage no specific treatment is indicated. The serum biological half-life of clindamycin is 2.4 hours. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

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: Anti-infectives for treatment of acne, ATC Code: J01FF01.

Mechanism of action
Dalacin C is a lincosamide antibiotic with a primarily bacteriostatic action against gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as Dalacin C bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit the early stages of protein synthesis. The action of Dalacin C is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Although Dalacin C is inactive *in vitro*, rapid *in vivo* hydrolysis converts this compound to the antibacterially active clindamycin. At usual doses, clindamycin exhibits bacteriostatic activity *in vitro*.

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

Resistance
Resistance to clindamycin is most often due to mutations at the rRNA antibiotic binding site or methylation of specific nucleotides in the 23S RNA of the 50S ribosomal subunit. These alterations can determine *in vitro* cross resistance to macrolides and streptogramins B (MLSB phenotype). Resistance is occasionally due to alterations in ribosomal proteins. Resistance to clindamycin may be inducible by macrolides in macrolide-resistant bacterial isolates.

Inducible resistance can be demonstrated with a disk test (D-zone test) or in broth. Less frequently encountered resistance mechanisms involve modification of the antibiotic and active efflux. There is complete cross resistance between clindamycin and lincomycin. As with many antibiotics, the incidence of resistance varies with the bacterial species and the geographical area. The incidence of resistance to clindamycin is higher among methicillin-resistant staphylococcal isolates and penicillin-resistant pneumococcal isolates than among organisms susceptible to these agents.

Most gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to Dalacin C. Dalacin C demonstrates cross-resistance with lincomycin. When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly developed resistance to Dalacin C. The mechanisms for resistance are the same as for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein and in a few staphylococcal isolates enzymatic inactivation by a plasmid-mediated adenyltransferase.

Clinical efficacy against specific pathogens
Dalacin C has been shown to have *in vitro* activity against most isolates of the following organisms:

Aerobic bacteria
Gram-positive bacteria

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

Gram-negative bacteria

- *Chlamydiatrachomatis*

Anaerobic bacteria
Gram-positive bacteria

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

Gram-negative bacteria

- *Bacteroides* spp.
- *Fusobacterium* spp.
- *Gardnerella vaginalis*
- *Prevotella* spp.

Fungi

- *Pneumocystis jirovecii*

Protozoans

- *Toxoplasma gondii*
- *Plasmodium falciparum*

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Clindamycin and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx
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 in at least some types of infections is questionable. Particularly in severe infections or therapy failure microbiological diagnosis with verification of the pathogen and its susceptibility to clindamycin is recommended.

5.2 Pharmacokinetic properties

Absorption
Serum level studies with a 150mg oral dose of Dalacin C in 24 normal adult volunteers showed that Dalacin C was rapidly absorbed after oral administration. An average peak serum level of 2.5 mcg/mL was reached in 45 minutes: serum levels averaged 1.51 mcg/mL at 3 hours and 0.70 mcg/mL at 6 hours. Absorption of an oral dose is virtually complete (90%) and the concomitant administration of food does not appreciably modify the serum concentrations; serum levels have been uniform and predictable from person to person and dose to dose. Serum levels studies following multiple dose of Dalacin C for up to 14 days show no evidence of accumulation or altered metabolism of drug. Serum half-life of Dalacin C is increased slightly in patients with markedly reduced renal function. Haemodialysis and peritoneal dialysis are not effective in removing Dalacin C from the serum. Concentrations of Dalacin C in the serum increased linearly with increased dose. Serum levels exceed the MIC (minimum inhibitory concentrations) for most indicated organisms for at least six hours following administration of the usually recommended doses.

Distribution
Clindamycin is widely distributed in body fluids and tissues including bone, but it does not reach the cerebrospinal fluid in significant concentrations. It diffuses across the placenta into the foetal circulation and appears in breast milk. Concentrations in human breast milk have been reported to be up to 3.8 µg/mL shortly after a 600 mg IV dose, falling to about 1 µg/mL at about 2 h. The Cmax after oral dosing is not known but milk levels up to 1.2 µg/mL have been reported after a 150 mg oral dose. High concentrations occur in bile.

Biotransformation
In vitro studies in human liver and intestinal microsomes indicated that clindamycin is predominantly oxidized by CYP3A4, with minor contribution from CYP3A5, to form clindamycin sulfoxide and a minor metabolite, N-desmethylclindamycin. The average biological half-life is 2.4 hours.

Elimination
Approximately 10% of the bioactivity is excreted in the urine and 3.6% in the faeces; the remainder is excreted as bioinactive metabolites. Doses of up to 2 grams of Dalacin C per day for 14 days have been well tolerated by healthy volunteers, except that the incidence of gastrointestinal side effects is greater with the higher doses. No significant levels of Dalacin C are attained in the cerebrospinal fluid, even in the presence of inflamed meninges. Pharmacokinetic studies in elderly volunteers (61-79 years) and younger adults (18-39 years) indicate that age alone does not alter Dalacin C pharmacokinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentrations time curve) after IV administration of Dalacin C phosphate. After oral administration of Dalacin C, elimination half-life is increased to approximately 4.0 hours (range 3.4-5.1 h) in the elderly compared to 3.2 hours (range 2.1-4.2 h) in younger adults. The extent of absorption however, is not different between age groups and no dosage alteration is necessary for the elderly with normal hepatic function and normal (age-adjusted) renal function.

Obese paediatric patients aged 2 to 18 years and obese young adults aged 18 to 20 years:
An analysis of pharmacokinetic data in paediatric patients (2 to 18 years) and young adults (18 to 20 years) demonstrated that the clearance and volume of distribution of clindamycin, when normalized to total body weight, are comparable between obese and non-obese patients.

5.3 Preclinical safety data

There is no evidence of teratogenic effect in animals, nor to date in man.

Carcinogenicity
Long term studies in animals have not been performed with Dalacin C to evaluate carcinogenic potential.

Mutagenicity
Genotoxicity tests performed included a rat micronucleus test and an Ames Salmonella reversion test. Both tests were negative.

Reproductive toxicity
Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the highest recommended adult human dose based on mg/m^2) revealed no effects on fertility or mating ability.

In oral embryo 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Talc
Magnesium stearate

Capsules:
Gelatin
Titanium dioxide (E171)

Printing Ink:
Shellac
Soya lecithin
Dimeticone (Antifoam DC 1510)
Black iron oxide
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Dalacin C 150mg Hard Capsules are available in blister packs (aluminium foil/PVC) of 24 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
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Dublin 4
D04 K7N3
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8 MARKETING AUTHORISATION NUMBER

PA0822/120/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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