Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 150 mg Capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin.
Excipient(s) with known effect:
Each capsule contains 230 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
A capsule with a lavender body and maroon cap imprinted with CL 150 in white.

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.

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 Clindamycin Capsules 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.

Pediatric 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.

Clindamycin 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 orally with water. Clindamycin Capsules may be taken without regard to food.
Clindamycin Capsules should always be swallowed whole and washed down with a full glass of water while in an upright position.

4.3 Contraindications

Hypersensitive to clindamycin, lincomycin, or any of the excipients listed in section 6.1.

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).

Clostridium Difficile associated diarrhoea
Clindamycin Capsules 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 *Clostridium difficile*) is the principal cause of antibiotic-associated colitis. These studies also indicate that this toxigenic clostridium 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 *Clostridium difficile*. This has been reported with use of nearly all antibacterial agents, including clindamycin. *Clostridium 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".

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 Clindamycin Capsules 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.

Cross Resistance
Attention should also be paid to the possibility of cross resistance to 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.Clindamycin Capsules should not be prescribed concurrently with erythromycin.

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 fetus 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	Very Common	Common ≥ 1/100	Uncommon ≥ 1/1 000	Rare ≥ 1/10 000 to	Very Rare	Not Known (cannot be estimated

	≥ 1/10	to < 1/10	to <1/100	<1/1 000	< 1/10 000	From available data)
Infections and infestations		pseudomembranous colitis*#				*clostridium difficile* colitis*, Vaginal infection*
Blood and Lymphatic System Disorders						Agranulocytosis* Leukopenia*, Neutropenia* Thrombocytopenia* Eosinophilia
Immune System Disorders						Anaphylactic shock*, Anaphylactoid Reactions*, anaphylactic reaction*, hypersensitivity*
Nervous System Disorders						Dysgeusia
Gastrointestinal Disorders		Abdominal pain, Diarrhoea	Nausea, Vomiting			Oesophageal ulcer*‡ Oesophagitis*‡
Hepatobiliary Disorders						Jaundice*
Skin and Subcutaneous Tissue Disorders			Rash maculopapular, Urticaria			Toxic epidermal Necrolysis (TEN)*, Steven Johnson syndrome (SJS)*, drug reaction with eosinophilia and systemic symptoms (DRESS)*, Acute generalized exanthematous pustulosis (AGEP*), angioedema*, Erythema multiforme* Dermatitis exfoliative* Dermatitis bullous* Rash Morbilliform* Pruritus
Renal and urinary disorders						Acute kidney injury#
Investigations		Liver function test abnormal				

* ADR identified post-marketing.
‡ ADRs apply only to oral formulations.
# 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@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
Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action. against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin 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 clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.
Although Clindamycin 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.

Pharmacodynamic effects
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 Clindamycin. Clindamycin demonstrates cross-resistance with lincomycin. When tested by in vitro methods, some staphylococcal strains originally resistant to erythromycin rapidly developed resistance to Clindamycin. 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 enzymic inactivation by a plasmid-mediated adenyltransferase.

<u>Antimicrobial activity</u>
Clindamycin has been shown to have *in vitro* activity against isolates of the following organisms:

<u>Aerobic bacteria</u>
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

- *Chlamydia trachomatis*

Anaerobic bacteria

Gram-positive bacteria

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

Gram-negative bacteria

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

Fungi

o *Pneumocystis jirovecii*

Protozoans

o *Toxoplasma gondii*

o *Plasmodium falciparum*

Breakpoints
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.
Resistance is usually defined by susceptibility interpretive criteria (breakpoints) established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for systemically administered antibiotics.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints are presented below.

Table 1. EUCAST Susceptibility Interpretive Criteria for Clindamycin

	MIC breakpoints (mg/L)		Zone diameter breakpoints (mm)[a]	
Organism	**S ≤**	**R >**	**S ≥**	**R <**
Staphylococcus spp.	0.25	0.5	22	19
Streptococcus Groups A, B, C and G	0.5	0.5	17	17
Streptococcus pneumoniae	0.5	0.5	19	19
Viridans group streptococci	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 µg of clindamycin NA=not applicable; S=susceptible; R=resistant				

EUCAST QC ranges for MIC and disk zone determinations are in the table below.

Table 2. EUCAST Acceptable Quality Control (QC) Ranges for Clindamycin to be Used in Validation of Susceptibility Test Results

QC Strain	**Minimum Inhibitory Concentration Range (mcg/mL)**	**Disk Diffusion Range (Zone Diameters in mm)**
Staphylococcus aureus ATCC 29213	0.06–0.25	23-29
Streptococcus pneumoniae ATCC 49619	0.03–0.125	22-28

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5.2 Pharmacokinetic properties

Absorption
Serum level studies with a 150mg oral dose of clindamycin in 24 normal adult volunteers showed that clindamycin 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 clindamycin for up to 14 days show no evidence of accumulation or altered metabolism of drug. Serum half-life of clindamycin is increased slightly in patients with markedly reduced renal function. Haemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum. Concentrations of clindamycin 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 bones. 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 clindamycin 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 clindamycin 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 clindamycinpharmakinetics (clearance, elimination half-life, volume of distribution, and area under the serum concentrations time curve) after IV administration of clindamycin phosphate. After oral administration of clindamycin, 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.

Carcinogenesis:
Long term studies in animals have not been performed with clindamycin to evaluate carcinogenic potential.

Mutagenesis:
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/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents
Lactose Monohydrate
MaizeStarch
Magnesium Stearate
Purified Talc
Capsule Body
Gelatin
Erythrosin (E127)
Indigo carmine FD&C Blue (E132)
Capsule Cap
Gelatin
Erythrosin (E127)
Indigo carmine FD&C Blue (E132)
Titanium dioxide (E171)
Printing Ink
Shellac,
propylene Glycol (E1520)
titanium dioxide (E171)
ethanol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs composed of PVC / PE / PVdC aluminium foil; pack sizes: 4, 8, 16, 20, 24, 30, 32, 40 and 100. Polypropylene containers with polyethylene tamper evident lids; pack size: 100. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Chanelle Medical Unlimited Company
Dublin Road
Loughrea
Co. Galway
H62 FH90
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0688/044/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 4th July 2008

10 DATE OF REVISION OF THE TEXT

July 2024