SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clindamycin Actavis 150 mg hard capsules
Clindamycin Actavis 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin.
Each capsule contains clindamycin hydrochloride equivalent to 300 mg clindamycin.

Excipient with known effect:
One capsule contains 33.9 mg lactose (see section 4.4).
One capsule contains 67.8 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
Size '1' (19.3 mm) hard gelatin capsule with opaque white cap and opaque white body imprinted with 'A714' on cap with black ink.
Size '0' (21.4 mm) hard gelatin capsule with opaque white cap and opaque white body imprinted with 'A718' on cap with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the following indications, Clindamycin Actavis should be reserved for patients hypersensitive to betalactam antibiotics or where these are unsuitable for other reasons:
- Pharyngotonsillitis
- Skin and soft tissue infections, including recurrent hidroadenitis

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

4.2 Posology and method of administration

Posology

Adults
300 mg twice daily or 150 mg 3-4 times daily.
If necessary, the dose may be increased to 300 mg 3-4 times daily.

Paediatric population
15 mg/kg per day divided into 3 doses.
Children weighing 30-45 kg can be given 150 mg 3 times daily.
The maximum dose is 20 mg/kg/day. This dose should be administered 4 times daily.

Clindamycin Actavis capsules are not suitable for children who cannot swallow the capsules whole or where an appropriate dosage is not possible with the available strengths. It may be necessary to use an alternative formulation of clindamycin.

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.

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.

Treatment monitoring
During long-term treatment, liver and kidney function tests should be performed and haematological parameters monitored. If diarrhoea occurs during treatment, the preparation should be discontinued. If rapid improvement does not occur, testing for *Clostridium difficile* should be performed.

Method of Administration
Clindamycin capsules are given orally. The capsules should be taken whole with at least half a glass of liquid and in an upright position (i.e. sitting or standing).
The capsules must not be opened due to the risk of oesophageal injury.
Absorption is not affected by concomitant food intake.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Serious cases of hypersensitivity reactions and severe skin reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustulosis (AGEP) have been reported in patients treated with clindamycin. If hypersensitivity or severe skin reaction occurs, clindamycin should be discontinued and appropriate treatment initiated (see sections 4.3 and 4.8).

Treatment with antibacterial agents alters the normal flora of the colon, giving rise to overgrowth of *Clostridium difficile*. This has been reported with the use of almost all antibacterial agents, including clindamycin. *Clostridium difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhoea (CDAD) and are the primary cause of “antibiotic-associated colitis”.

It is important to consider the diagnosis of CDAD in patients who develop diarrhoea after administration of antibacterial agents. This can progress to colitis, including pseudomembranous colitis (see section 4.8), which can range from mild to life-threatening 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.

Elderly, hospitalised and patients with underlying diseases are more likely to be affected than others. Patients should always be informed of the risk of *Clostridium difficile* infection associated with clindamycin treatment and also advised to contact the treating physician if diarrhoea occurs. Note that diarrhoea and pseudomembranous colitis may occur a long time (> 1 month) after clindamycin treatment is stopped.

Clindamycin does not diffuse into cerebrospinal fluid, and it should therefore not be used in the treatment of meningitis.

In case of prolonged treatment, function tests of the liver and kidneys should be performed.

Acute kidney injury, including acute renal failure, has been reported in rare cases. For patients with a history of renal impairment or concomitant use of nephrotoxic drugs, monitoring of renal function should be considered (see section 4.8).

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

Excipients

Lactose
Clindamycin Actavis capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially ´sodium-free`.

4.5 Interaction with other medicinal products and other forms of interaction

Antagonism (inducible resistance) has been demonstrated between clindamycin and erythromycin *in vitro*, more specifically for certain macrolide-resistant bacterial isolates. Due to the possible clinical significance of this interaction, these two medicinal products should not be administered concomitantly.

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other muscle relaxants. It should therefore be used with caution in patients receiving such agents.

Clindamycin is metabolised primarily by CYP3A4 and to a lesser extent by CYP3A5 to the major metabolite clindamycin sulfoxide and the minor metabolite N-desmethylclindamycin. CYP3A4 and CYP3A5 inhibitors may therefore increase plasma concentrations of clindamycin. Some examples of strong CYP3A inhibitors are itraconazole, voriconazole, clarithromycin, telithromycin, ritonavir and cobicistat. Caution should be exercised when clindamycin is used with strong CYP3A4 inhibitors. Inducers of these enzymes may increase clearance of clindamycin, resulting in decreased plasma concentrations. In a prospective study of orally administered clindamycin, approximately 80% lower trough levels of clindamycin were seen when given 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, the patient should be monitored for impaired treatment effect.

In vitro studies show that clindamycin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2E1 or CYP2D6. Any clinically significant effects of clindamycin on concomitantly administered drugs metabolised by these CYP enzymes are therefore unlikely. Based on *in vitro* data, clindamycin may inhibit CYP3A4 in the intestine when administered orally. The exposure of orally administered CYP3A4 substrates, e.g. dihydroergotamine, ergotamine, ergometrine, midazolam, triazolam, amiodarone, quinidine, cisapride, pimozide, alfuzosin, simvastatin, lovastatin, and sildenafil, may thus be increased if they are co-administered with orally administered clindamycin. Caution should be exercised when oral clindamycin is used with orally administered CYP3A4 substrates, especially those with a narrow therapeutic window.

Vitamin K antagonists
Increased coagulation test results (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). Therefore, coagulation test results should be closely monitored in patients treated with vitamin K antagonists.

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 (see section 5.3). Animal reproduction studies are not always predictive of human response.

Clindamycin crosses the placenta in humans. After repeated doses of the medicinal product, the concentration of clindamycin in the amniotic fluid was approximatley 30 % of the maternal blood concentration.

In clinical trials with pregnanat 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 pregnant women only if clearly needed.

Breastfeeding
Clindamycin is excreted in breast milk at various concentrations in the range <0.5-3.8 μg/ml. As clindamycin may cause serious adverse reactions in the intestinal flora in breastfed children, such as diarrhoea, blood in the stools or skin rashes, the use of systemically administered clindamycin in breastfeeding mothers is not recommended and a decision should be made whether to discontinue breastfeeding or to choose another treatment option. The developmental and health benefits of breastfeeding should be considered in conjunction with the mother's clinical need for clindamycin.

Fertility
Fertility studies in rats treated orally with clindamycin revealed no effects 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

Gastrointestinal side effects occur in about 8% of patients, mainly diarrhoea.

The table below lists the adverse reactions identified in clinical trials and during post-marketing surveillance by system organ class and frequency.
Adverse reactions identified during post-marketing experience are included in italics.

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);
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	Not Known (cannot be estimated from available data)
Infections and infestations	*Pseudomembranous colitis* (see section 4.4)		*Clostridium difficile colitis* (see section 4.4), *Vaginal infection*
Blood and Lymphatic System Disorders			*Agranulocytosis, Leukopenia, Neutropenia, Thrombocytopenia,* Eosinophilia
Immune System Disorders			*Anaphylactic shock, Anaphylactoid reactions, Anaphylactic reactions, Hypersensitivity*
Nervous System Disorders			Dysgeusia (altered taste)
Gastrointestinal Disorders	Abdominal pain, Diarrhoea	Nausea, Vomiting	*Oesophageal ulcer, Oesophagitis*
Hepatobiliary Disorders			*Jaundice*
Skin and Subcutaneous Tissue Disorders		Maculopapular rash, Urticaria	*Toxic epidermal necrolysis, Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS), Acute generalised exanthematous pustulosis (AGEP),* Erythema multiforme, *Angiooedema, Dermatitis exfoliative, Dermatitis bullous, Rash morbilliform,* Pruritis
Renal and urinary disorders			Acute kidney injury (see section 4.4)
Investigations	Liver function tests abnormal		

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

Clindamycin has a low acute toxicity, but there is limited experience of overdose. Symptoms of overdose include nausea, vomiting and diarrhoea. Allergic reactions may occur. Ventricular emptying should be performed if warranted. Treatment with charcoal and symptomatic therapy is recommended.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lincosamides, ATC code: J01FF01

Mechanism of action
Clindamycin is a lincosamide antibiotic that inhibits bacterial protein synthesis. It binds to the 50S subunit of ribosomes and affects both the ribosome transformation and translation processes. Clindamycin is primarily bacteriostatic but can also have a bactericidal effect depending on the sensitivity of the bacteria and growth conditions.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.

Pharmacokinetic/pharmacodynamic relationship
The antibacterial effect of clindamycin is essentially dependent on the time that the active substance exceeds the minimum inhibitory concentration (MIC) of the infecting organism (%T>MIC). Plasma levels exceeded the MIC for most microorganisms for which clindamycin is indicated for at least 6 hours after administration of the normally recommended dose.
Treatment with antibacterial agents affects the normal intestinal flora and may cause overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated colitis.

Mechanism of resistance
Resistance to clindamycin is mainly due to changes in the bacterial binding sites to which clindamycin binds. In most organisms that are usually sensitive to clindamycin, the main mechanism of resistance is a change in the binding site of the ribosomal RNA molecule for the 23S subunit, either by chemical change or by mutation. This change reduces the target's antibiotic affinity. Since lincosamide, macrolide and streptogramin B antibiotics bind to the same target and have overlapping binding sites, this change results in cross-resistance between these three classes of antibiotics (MLS_B phenotype). Resistance to clindamycin can be inducible by macrolides in macrolide-resistant bacterial isolates. Less common resistance mechanisms are antibiotic modification and active transport.

Breakpoints
The EUCAST recommended minimum inhibitory concentration (MIC) breakpoints for clindamycin, separating susceptible from susceptible increased exposure organisms and susceptible increased exposure from resistant organisms are presented in the below table for MIC testing (mg/l).

EUCAST clinical MIC breakpoints for clindamycin (Version 13.0, 2023-01-01):

Pathogen	**Susceptible**	**Resistant**
Staphylococcus spp. [1)]	≤ 0,25 mg/l	> 0,25 mg/l
Streptococcus groups A, B, C, G [1), 2)]	≤ 0,5 mg/l	> 0,5 mg/l
Streptococcus pneumoniae [1)]	≤ 0,5 mg/l	> 0,5 mg/l
Viridans group streptococci [1)]	≤ 0,5 mg/l	> 0,5 mg/l
Bacteroides spp.	≤ 4 mg/l [3)]	> 4 mg/l [3)]

Prevotella spp.	≤ 0.25 mg/l	> 0.25 mg/l
Fusobacterium necrophorum	≤ 0.25 mg/l	> 0.25 mg/l
Clostridium perfingens	≤ 0.25 mg/l	> 0.25 mg/l
Cutibacterium acnes	≤ 0.25 mg/l	> 0.25 mg/l

1) Inducible clindamycin resistance can be detected by antogonism of clindamycin activity by a macrolide agent. If no antagonism is detected, clindamycin sensitivity is present. If antagonism is detected, clindamycin resistance is present.
2) The clinical importance of inducible clindamycin resistance in combination treatment of severe *S. pyogenes* infections is not known.
3) Many Bacteroides species when without resistance mechanisms have clindamycin MIC-values of 1, 2 and 4 and some species even higher MICs. All other species with breakpoints for clindamycin have wild type MIC values and breakpoints on or below 0.5 mg/L (for example staphylococci, streptococci, *S. pneumoniae*). Most infections with Bacteroides involve aerobic and anaerobic bacteria and therapeutic traditions mostly call for combination therapy.

These data have been produced in part under ECDC service contracts and made available by EUCAST at no cost to the user and can be accessed on the EUCAST website www.eucast.org. EUCAST recommendations are frequently updated and the latest versions are available at www.eucast.org or www.eucast.org/clinical_breakpoints/.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desireable, particularly when treating severe infections. As necessary, expert advice should be sought where the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

***In vitro* susceptibility of micro-organsims to clindamycin**
Commonly Susceptible Species **Gram–positive bacteria** *Staphylococcus aureus* (methicillin-sensitive isolates) *Staphylococcus* spp. *Streptococcus pneumoniae* *Streptococcus* spp. **Anaerobic bacteria** *Bacteriodes fragilis*-group *Bacteroides melaninogenicus-group* *Fusobacterium* spp. *Prevotella* spp. *Peptostreptococcus* spp. *Peptococcus spp.* *Propionibacterium acnes* *Clostridium perfringens* *Eubacterium* spp. *Actinomyces* spp.
Species for which acquired resistance may be a clinical problem Methicillin resistant *Staphylococcus aureus (MRSA)* - Coagulase negative *Staphylococcus* spp. - Meticillin-sensitive *Staphylococcus aureus (MSSA)* - C*lostridium* spp. (except *C. perfringens*) - *Bacteroides* spp. - *Streptococcus pneumoniae*

- *Streptococcus pyogenes* (β-haemolytic streptococcus group A)

Naturally resistant organisms

Gram–positive aerobes
Enterococcus spp.

Gram–negative aerobes
Most species

Gram–positive anaerobes
Clostridium difficile

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 highly distributed intracellularly (in body fluids and tissues including bone). Intracellular concentration is 10-50 times higher than the extracellular concentration.
No significant levels of clindamycin have been measured in cerebrospinal fluids, despite inflamed meninges. Clindamycin is 92-94 % plasma protein bound and has good penetration into most tissues. The substance crosses the placenta but not a normal blood-brain barrier.

Metabolism
The majority of clindamycin is metabolised. *In vitro* studies showed that clindamycin is metabolised mainly by CYP3A4 and to a lesser extent by CYP3A5, forming clindamycin sulfoxide and a minor metabolite N-desmethylclindamycin.

Elimination
Clindamycin is excreted even in active form mainly via bile (10 %) and faeces (3,6 %) but to some extent also via urine; the remaining amount is excreted as biologically inactive metabolites.
After oral administration, the half-life is approximately 2.4 hours.

Special patient groups

Elderly
Pharmacokinetic studies in elderly volunteers (61-79 years) and young adults (18-39 years) indicate that age alone does not affect the pharmacokinetic properties of clindamycin after intravenous administration of clindamycin phosphate. Following oral administration of clindamycin, the half-life increases to approximately 4 hours (range 3.4-5.1 hours) in the elderly compared to 3.2 hours (range 2.1-4.2 hours) in young adults. Absorption rates show no differences between the different age groups. Dose modification is not necessary for elderly with normal hepatic and renal function.

Renal impairment
Serum half-life is slightly increased in patients with severely reduced renal function. Haemodialysis and peritoneal dialysis are not effective methods of removing clindamycin from serum.

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.

Paediatric patients and young adults with obesity
An analysis of pharmacokinetic data in paediatric patients with obesity treated with intravenous clindamycin aged 2 to younger than 18 years and adults with obesity aged 18 to 20 years showed that clindamycin clearance and volume of distribution, normalized by total body weight, are comparable regardless of obesity.

5.3 Preclinical safety data

Carcinogenicity
No long-term studies of clindamycin have been performed in animals to assess carcinogenic potential.

Mutagenicity
Genotoxicity tests in the form of a rat micronucleus test and an Ames test have been performed, both with negative results.

Reproductive toxicity
Fertility studies in rats treated orally with up to 300 mg/kg/day (approximately 1.1 times the maximum recommended human dose calculated as mg/m^2) did not show any effects on fertility or mating ability.

In oral embryo-fetal development studies in rats and subcutaneous embryo-fetal development studies in rats and rabbits, no development of toxicity was observed except at doses that caused maternal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
Lactose
Corn starch
Talc
Magnesium stearate

Capsule cap and body
Titanium dioxide (E171)
Gelatin
Water
Sodium lauril sulfate

Printing ink
Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

No special storage conditions.

6.5 Nature and contents of container

Clindamycin Actavis 150 mg capsules are available in blister packs (clear PVC/Aclar film / aluminimum foil) of
Clindamycin Actavis 300 mg capsules are available in blister packs (clear PVC/Aclar film / aluminimum foil) of
12, 15, 16, 20, 24, 30, 32, 40, 100 and 104 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

14/03/2023

[To be completed nationally]