1. NAME OF THE MEDICINAL PRODUCT

Clindamycin EQL Pharma 150 mg capsules, hard
Clindamycin EQL Pharma 300 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One hard capsule contains:
Clindamycin hydrochloride, equivalent to 150 mg or 300 mg clindamycin.

Excipients with known effect: one hard capsule contains lactose monohydrate of 0.6 mg or 1 mg (see section 4.4).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules, hard
150 mg: hard cylindrical gelatin capsules, 17,5 mm with blue body and blue cap.
300 mg: hard cylindrical gelatin capsules, 21,7 mm with white body and blue cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In the following indications, Clindamycin EQL Pharma should be reserved for patients who are hypersensitive to beta-lactam antibiotics or where they are unsuitable for other reasons:
Pharyngotonicillitis. Skin and soft tissue infections, including recurrent hidroadenitis.

4.2 Posology and method of administration

Dosage
Adults: 300 mg 2 times daily or 150 mg 3-4 times daily. If necessary, the dose can be increased to 300 mg 3-4 times daily.

Pediatric population: The capsules should only be used for children who are able to swallow capsules.15 mg / kg and day divided into 3 doses. Children weighing 30 - 45 kg are given 150 mg 3 times a day. The maximum dose is 20 mg / kg / day. At this dose, dosing should be done 4 times daily. As capsules cannot always be used to give the exact dose in mg / kg as desired in the treatment of children, it may be necessary to use other products and formulations with clindamycin instead.

Treatment control: In long-term treatment, liver and renal function tests should be performed and the blood image monitored. If diarrhea occurs during treatment, the product should be discontinued. If rapid improvement does not occur, study on *Clostridium difficile* should be performed.

Method of administration
The capsules should be taken whole with at least ½ glass of liquid and in upright position (not in the lying position). The capsules should not be divided due to the risk of oesophageal damage. Absorption is not affected by simultaneous food intake.

4.3 Contraindications

Known 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

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 generalized exantematous pustulosis (AGEP) have been reported in patients treated with clindamycin. If hypersensitivity or severe skin reaction occurs, clindamycin should be discontinued and adequate treatment initiated (see section 4.3 and section 4.8).

Treatment with antibacterial drugs changes the normal flora in the colon, and causes overgrowth of *Clostridium difficile*. This has been reported with the use of almost all antibacterial drugs, including clindamycin. *Clostridium difficile* produces toxins A and B that contribute to the development of *Clostridium difficile*-associated diarrhea (CDAD) and are the primary cause of "antibiotic-associated colitis".

It is important to consider the diagnosis of CDAD in patients receiving diarrhea after administration of antibacterial drugs. This may develop into colitis, including pseudomembranous colitis (see section 4.8), which may vary from mild to life threatening colitis. If antibiotic-associated diarrhea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial drugs, including clindamycin, should be discontinued and appropriate treatment measures immediately instituted. Drugs that inhibit peristalsis are contraindicated in this situation.

Elderly, hospitalized and patients with underlying diseases are affected to a greater extent than others. Patients should always be informed of the risk of infection with *Clostridium difficile* in association with clindamycin and also be advised to contact the treating physician if diarrhea occurs. Note that diarrhea and pseudomembranous colitis may occur for a long time (> 1 month) after the completion of clindamycin treatment.

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

In long-term treatment, liver and renal function tests should be performed.

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)

The use of clindamycin may cause overgrowth of organisms that are not sensitive to clindamycin, especially yeast fungus.

This medicine 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 has been shown to have neuromuscular blocking properties that can enhance the effect of other muscle relaxants. Clindamycin EQL Pharma should therefore be used with caution in patients treated with such products. Antagonism between clindamycin and erythromycin has been demonstrated *in vitro*. Due to the possible clinical significance of this interaction, these two drugs should not be given concurrently.
Clindamycin is primarily metabolised by CYP3A4 and, to a lesser extent, CYP3A5 to the major metabolite clindamycin sulfoxide and the smaller metabolite N-desmethylclindamycin. Therefore, CYP3A4 and CYP3A5 inhibitors may increase the plasma concentrations of clindamycin. 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 clindamycin clearance, resulting in decreased plasma concentrations. In a prospective study of orally administered clindamycin, approximately 80% lower valence of clindamycin was 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, 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 co-administered drugs metabolised by these CYP enzymes are therefore unlikely. Based on *in vitro* data, clindamycin, when administered orally, may inhibit CYP3A4 in the intestine. The exposure of orally administered CYP3A4 substrates, eg dihydroergotamine, ergotamine, ergometrine, midazolam, triazolam, amiodarone, quinidine, cisapride, pimozide, alfuzosin, simvastatin, lovastatin, and sildenafil, may increase if administered together 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 monitored carefully in patients treated with vitamin K antagonists.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oral and subcutaneous reproductive toxicity studies in rats and rabbits showed no evidence of impaired fertility or fetal injury caused by clindamycin, except at doses that caused maternal toxicity (see section 5.3). Reproductive studies on animals are not always predictive of effects on humans

Clindamycin passes the placental barrier in humans. After repeated doses of the drug product the estimated concentration in the amniotic fluid represents approximately 30% of the plasma levels measured in the mother.

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

Clindamycin should not be used during pregnancy unless clearly needed.

Breast-feeding

Clindamycin passes into breast milk in such amounts that there is a risk of affecting the child present even at therapeutic doses. Oral and parenterally administered clindamycin has been reported to occur in breast milk at a concentration ranging from 0.7 to 3.8 μg / ml. Due to the risk of serious adverse reactions in breast-feeding children, breast-feeding mothers should not take clindamycin.

Fertility
Fertility studies conducted in rats treated with oral clindamycin showed no effects on fertility or reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines

Clindamycin has no or negligible effect on the ability to drive and use machines.

4.8 Undesirable effects

Gastrointestinal adverse events occur in approximately 8% of patients, mainly diarrhea.

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

The following terminology has been used for the classification of undesirable effects in terms of frequency: 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 (the frequency cannot be estimated from the available data).
In 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)**	**Not known (frequency cannot be estimated from the 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 Thrombocytosis Eosinophilia
Immune system disorders				Anaphylactic chock Anaphylactic reaction Anaphylactoid reaction Hypersensitivity reactions
Nervous system disorders				Dysgeusia (changed taste)
Gastrointestinal disorders	Abdominal pain Diarrhea	Nausea Vomiting		Oesophageal ulcer Oesophagitis
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders		Maculopapular rash Urticaria		Toxic epidermal necrolysis Stevens-Johnson syndrom Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

				Acute Generalised Exanthematous Pustulosis (AGEP) Erythema multiforme Angiooedema Exfoliative dermatitis Bullous dermatitis Morbilliform rash Pruritus
Surveys	Abnormal hepatic values			
Renal and urinary disorders				Acute kidney injury*

* See section 4.4

Fungal infections in the mouth and abdomen may occur.

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

Low acute toxicity but limited experience of overdose. Symptoms of overdose are nausea, vomiting, diarrhea. Allergic reactions may occur. Ventricular emptying should be performed if warranted. Treatment with carbon as well as symptomatic therapy is recommended.
Haemodialysis and peritoneal dialysis are not effective methods for eliminating clindamycin from the serum.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lincosamide antibiotics.
ATC code: J01FF01

Mechanism of action

Clindamycin is a linkosamide antibiotic that inhibits bacterial protein synthesis. It binds to the ribosomes 50S subunit and affects both the ribosome formation and the translation process. Clindamycin is predominantly bacteriostatic but may also have bactericidal effects due to the sensitivity and growth conditions of the bacteria. Clindamycin hydrochloride is active both in vitro and in vivo. Clindamycin phosphate and clindamycin palmitate are inactive in vitro but rapidly hydrolyzed in vivo to the active base.

Relationship between pharmacokinetics and pharmacodynamics
The antibacterial effect of clindamycin is mainly dependent on the time the active substance exceeds the minimum inhibitory concentration (MIC) of the infectious organism. Plasma levels exceeded MIC

for most microorganisms where clindamycin is indicated for at least 6 hours after administration of the usual recommended dose.
Treatment with antibacterial agents affects the normal intestinal flora and may cause clostridial overgrowth. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of antibiotic-associated colitis.

Mechanisms of resistance
Resistance to clindamycin is mainly due to changes in the bacterial binding sites that clindamycin binds to. In most organisms that are usually sensitive to clindamycin, the major resistance mechanism is a change in the binding site in the ribosomal RNA molecule of the 23S subunit, either by chemical change or by mutation. This change reduces the target's antibiotic affinity. Since linkosamide, macrolide and streptogramin B antibiotics bind to the same target and have overlapping binding sites, the change gives rise to cross-resistance between these three antibiotic classes. Uncommon resistance mechanisms are antibiotic modification and active transport. As with many antibiotics, the presence of resistance varies with organism and geographic. Information on local resistance conditions should be obtained through local microbiological laboratory.

Breakpoints
The following table contains breakpoints for minimum inhibition concentration (MIC) established by EUCAST (the European Committee on Antimicrobial Susceptibility Testing):

	S	R
Staphylococcus spp *Staphylococcus* spp.	≤ 0,25	> 0,5
Streptococcus group A, B, C, G	≤0,5	> 0,5
Streptococcus pneumoniae	≤ 0,5	> 0,5
Streptococci belonging to viridans-group	≤ 0,5	> 0,5
Grampositive anaerobes (except *C. difficile)*	≤ 4	> 4
Gramnegative anaerobes	≤ 4	> 4

Sensitivity
The prevalence of acquired resistance in one species may vary geographically and over time. Local information about resistance is therefore desirable, especially in the treatment of severe infections. Specialist help should be sought when needed when local prevalence is such that clindamycin usefulness is doubtful in at least some types of infections.

Infections caused by clindamycin resistant organisms have been reported in the European Union. The information below describes the approximate likelihood that a microorganism is clindamycin sensitive or not.

Commonly sensitive species
Gram-positive aerobics
Staphylococcus aureus (methicillin sensitive)
Staphylococcus spp.
Streptococcus pneumoniae
Streptococcus spp.

Anaerobes
Bacteroides 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
Meticillin-resistant *Staphylococcus aureus* (MRSA)
Coagulas negative *Staphylococcus* spp.
Meticillin-sensitive *Staphylococcus aureus* (MSSA)
Clostridium spp. (except *C. perfringens*)
Bacteroides spp.
Streptococcus pneumoniae
Streptococcus pyogenes (β-hemolytic streptococci group A)

Naturally resistant species
Gram-positive aerobics
Enterococcus spp.

Gram-negative aerobics
Most species

Gram-positive anaerobes
Clostridium difficile

5.2 Pharmacokinetic properties

Absorption
Absorption of an oral dose is complete (90%), and at the same time food intake does not significantly affect serum concentrations. Oral clindamycin is rapidly absorbed and reaches maximum plasma concentrations after about 45 minutes. Bioavailability is nonlinear and decreases with increasing dose. After administration of a 600 mg dose, the bioavailability approximates 53 ± 14%.

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

Metabolism
The majority of clindamycin is metabolized. In vitro studies showed that clindamycin is predominantly metabolised by CYP3A4 and, to a lesser extent, CYP3A5, with clindamycin sulfoxide and a smaller metabolite N-desmethyl clindamycin being formed.

Elimination
Clindamycin is also excreted in active form primarily via bile (10%) and feces (3.6%), but also via urine to some extent. Residual amount is excreted as biologically inactive metabolites.
After oral administration, the half-life is approximately 2.4 hours.

Special patient groups
Elderly: Pharmacokinetic studies among elderly volunteers (61-79 years) and adolescents (18-39 years) indicate that age alone does not affect the pharmacokinetic properties of clindamycin following intravenous administration of clindamycin phosphate. After oral administration of clindamycin, the half-life increases to approximately 4 hours (range 3.4 - 5.1 hours) in the elderly in comparison with 3.2 hours (range 2.1 to 4.2 hours) among young adults. The absorption rate shows no differences between the different age groups. Dose change is not necessary for elderly patients with normal liver and renal functions.

Renal impairment: Serum half-life increases slightly in patients with severe renal impairment. Hemodialysis and peritoneal dialysis are not effective methods for removing clindamycin from serum.

5.3 Preclinical safety data

Carcinogenicity:
No long-term studies of clindamycin have been performed on animals for the assessment of carcinogenic potential.

Mutagenesis:
Gentoxicity tests in the form of a rat micro-test and an Ames test have been performed, both with negative results.

Reproductive toxicity:
Rats fertility studies treated orally with up to 300 mg / kg / day (approximately 1.1 times the highest recommended human dose calculated as mg / m2) showed no effects on fertility or mating ability.

In oral studies on embryoetal development in rats and subcutaneous studies on embryoetal development in rats and rabbits, no development of toxicity was observed except at doses that caused toxicity in mother.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica, colloidal anhydrous
Lactose monohydrate
Gelatine
Maize starch
Magnesium stearate
Titanium dioxide (E171)
Indigo carmine (E132)

6.2 Incompatibilities

Not relevant.

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 PVC/ALU:
150 mg: 32 and 40 hard capsules
300 mg: 21 and 32 hard capsules

Bottle HDPE with cap of polypropylene:
150 mg: 45, 100 and 105 hard capsules
300 mg: 100 and 105 hard capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

2019-12-12

10. DATE OF REVISION OF THE TEXT

2021-12-01