SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 300mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 325.78 mg clindamycin hydrochloride equivalent to 300 mg clindamycin.

Excipient with known effect:

Each capsule contains 67.82 mg lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

Size '0' 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

Clindamycin is indicated for the treatment of severe infections (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

Where the required dosage cannot be achieved with capsules of this strength, there are other medicinal products containing clindamycin in capsules of other strengths on the market, which can be used.

Posology
Adults
Moderately severe infection: 150 - 300 mg every six hours
Severe infection: 1200 - 1800 mg daily in divided doses given every six to eight hours

Elderly
The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin hydrochloride are not altered by increased age. Analysis of data from clinical studies has not revealed any age-related increase in toxicity. Dosage requirements in elderly patients, therefore, should not be influenced by age alone.

Children: 3 - 6 mg/kg every six hours depending on the severity of the infection.

Clindamycin capsules are not suitable for children who are unable to swallow them whole. The capsules do not provide exact mg/kg doses therefore 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
Oral.Clindamycin capsules should always be swallowed whole with a full glass of water. Absorption of Clindamycin is not appreciably modified by the presence of food.

4.3 Contraindications

Clindamycin is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin or to any of the excipients listed in section 6.1.
Clindamycin should not be used in patients with existing diarrhoea.

4.4 Special warnings and precautions for use

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.

Warnings

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 generalised 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).

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 mucus. 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.

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

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

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

Periodic liver and kidney function tests should be carried out during prolonged therapy. Such monitoring is also recommended in neonates and infants.
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.

Excipients

Lactose
Clindamycin 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

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.

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
There was evidence of maternal toxicity and embryofetal toxicity in animal studies (see section 5.3). 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.

Breastfeeding
Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from <0.5 to 3.8µg/mL. Clindamycin has the potential to cause adverse effects on the breastfed infant's gastrointestinal flora such as diarrhoea or blood in the stool, or rash. If oral or intravenous clindamycin is required by a nursing mother, it is not a reason to discontinue breastfeeding, but an alternate drug may be preferred. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clindamycin and any potential adverse effects on the breastfed child from clindamycin or from the underlying maternal condition.

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.
Adverse reactions identified from 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**	**Rare ≥1/10 000 to <1/1 000**	**Not Known (cannot be estimated from available data)**
Infections and infestations	pseudomembranous colitis*#			*clostridium 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 generalised exanthematous pustulosis (AGEP)*, angioedema*, dermatitis exfoliative*, dermatitis bullous*, erythema multiforme, pruritus, rash morbilliform*
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 the Yellow Card Scheme at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: Lincocosamide antibiotics, ATC code: J01FF01

Mode 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 protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains. Although clindamycin phosphate is inactive in vitro, rapid in vivo hydrolysis converts this compound to the antibacterially active clindamycin.

Mechanism of resistance
Resistance to clindamycin usually occurs via macrolide-lincosamide-streptogramin B (MLS_B) type of resistance, which may be constitutive or inducible.

PK/PD relationship
Efficacy is related to the ratio of the area of the concentration-time curve of unbound antibiotic to the MIC for the pathogen (fAUC/MIC).

Breakpoints
The minimum inhibitory concentrations (MIC) breakpoints are as follows:
EUCAST
Staphylococci: sensitive ≤ 0.25 resistant > 0.5
Streptococci ABCG and *pneumoniae*: sensitive ≤ 0.5 resistant > 0.5
Gram positive anaerobes: sensitive ≤ 4 resistant > 4
Gram negative anaerobes: ≤ 4 resistant > 4

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.

Species
Susceptible
Gram-positive aerobes
*Staphylococcus aureus**
Staphylococcus epidermidis
Streptococcus pneumonia
Streptococcus pyogenes
Viridans streptococci

Anaerobes
Bacteriodes fragilis group
Prevotella formerly known as 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.

5.2 Pharmacokinetic properties

General characteristics of active substance
About 90% of a dose of clindamycin hydrochloride is absorbed from the gastro-intestinal tract; concentrations of 2 to 3 micrograms per ml occur within one hour after a 150 mg dose of clindamycin, with average concentrations of about 0.7 micrograms per ml after 6 hours. After doses of 300 and 600 mg peak plasma concentrations of 4 and 8 micrograms per ml, respectively, have been reported. Absorption is not significantly diminished by food in the stomach but the rate of absorption may be reduced.

Clindamycin is widely distributed in body fluids and tissues including bone, but it does not reach the csf in significant concentrations. It diffuses across the placenta into the foetal circulation and has been reported to appear in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90% of clindamycin in the circulation is bound to plasma

proteins. 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 half-life is 2 to 3 hours, although this may be prolonged in pre-term neonates and patients with severe renal impairment.

Clindamycin undergoes metabolism, presumably in the liver, to the active *N*-demethyl and sulfoxide metabolites, and also some inactive metabolites. About 10% of a dose is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Excretion is slow, and takes place over several days. It is not effectively removed from the blood by dialysis.

Characteristics in patients
No special characteristics. See section 4.4 "Special warnings and special precautions for use" for further information.

Obese paediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years. An analysis of pharmacokinetic data in obese paediatric patients aged 2 to less than 18 years and obese adults aged 18 to 20 years demonstrated that clindamycin clearance and volume of distribution normalized by total body weight are comparable regardless of obesity.

5.3 Preclinical safety data

There is no further preclinical data of relevance to the safety assessment beyond what has already been mentioned in this summary of product characteristics.

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 lauryl sulfate

Printing ink:

Shellac
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol (E1520)
Strong ammonia solution
Black iron oxide (E172)
Potassium hydroxide
Purified water

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 300 mg capsules are available in blister packs (clear PVC/Aclar film / aluminium foil)

Pack sizes: 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

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/2478

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/04/2022

10 DATE OF REVISION OF THE TEXT

20/01/2023