SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 300mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 300 mg clindamycin.
Excipients with known effect:
Each capsule contains 264 mg lactose monohydrate
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Hard gelatin capsule, lavender cap and lavender body with a marking 'C300' on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clindamycin is indicated for the treatment of:
Serious infections caused by anaerobic bacteria, including intra-abdominal infections, skin and soft tissue infections. As needed, clindamycin should be administered in conjunction with another antibacterial agent that is active against gram negative aerobic bacteria.
- Tonsillitis
- Dental infection

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

4.2 Posology and method of administration

Posology

Adults

The usual dose is 150-450 mg every six hours, depending on the severity of the infection.

Elderly patients

Dosage requirements in elderly patients should not be influenced by age alone

Paediatric population

The usual dose is 3-6 mg/kg every six hours depending on the severity of the infection (not to exceed the adult dose).

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

Clindamycin capsules are given orally. Capsules should always be swallowed whole and washed down with a full glass of water while in an upright position.

Absorption of Clindamycin capsules is not appreciably modified by the presence of food.

4.3 Contraindications

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

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).

Clindamycin should only be used in the treatment of serious infections and when the possible benefit of using clindamycin is considered to outweigh the risk of antibiotic- associated diarrhoea or colitis, which may progress to pseudomembraneous colitis, toxic megacolon and death. These intestinal complications are more likely to be severe and to become life-threatening in older patients or patients who are debilitated. Caution should also be used when prescribing clindamycin for individuals with a history of gastro-intestinal disease, especially colitis.

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.

If marked diarrhoea occurs during therapy, clindamycin should be discontinued immediately and appropriate diagnostic and therapeutic measures should be instituted. It should be noted that the onset of these intestinal complications of clindamycin treatment may be delayed until several weeks following the cessation of therapy. The most commonly implicated cause is an overgrowth of toxin-producing *Clostridium difficile* as a result of disruption of the bowel flora by clindamycin.

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.

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

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

Laboratory tests for renal and hepatic function should be carried out during prolonged therapy.

Close monitoring is also recommended in patients with renal or hepatic insufficiency and in neonates and infants, all of whom may require dose reduction and/or an extended interval between doses.

If therapy is prolonged, liver functions tests should be

performed. Acute kidney injury

Acute kidney injury, including acute renal failure, has been reported infrequently. Therefore, monitoring of renal function should be considered in patients receiving prolonged therapy, suffering from pre-existing renal dysfunction or taking concomitant nephrotoxic drugs (see section 4.8).

Prolonged administration of Clindamycin capsules, as with any anti-infective, may result in super – infection due to organism resistant to clindamycin.

Care should be observed in the use of Clindamycin capsules in atopic individuals.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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- resistance bacteria.

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

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 and therefore clindamycin should not be given in combination with macrolides or streptogramin antibacterial agents.

Neostigmine and pyridostigmine:
Clindamycin antagonises the effects of the above anticholinesterases.

Vaccines:
Oral typhoid vaccine is inactivated by concomitant administration of antibacterials. Thus, clindamycin should be avoided for 3 days before and after oral typhoid vaccination.

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.

4.6 Fertility, pregnancy and lactation

Fertility

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

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. There are inadequate data regarding the safety of Clindamycin in pregnancy. Therefore, Clindamycin should only be administered to pregnant women if the potential benefit is considered to outweigh the possible risk to the foetus.

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.

Lactation

Diarrhoea, fungus infection of the mucous membranes or other serious adverse events could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitivity should be borne in mind.

Orally and parenterally administered clindamycin has been reported to appear in human breast milk in ranges from 0.7 to 3.8µg/mL. Because of the potential for serious adverse reactions in nursing infants, clindamycin should not be taken by nursing mothers.

4.7 Effects on ability to drive and use machines

Clindamycin is not known to interfere with the ability to drive or operate machinery.

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** ≥1/1000 to <1/100	**Rare** ≥ 1/10000 to <1/1000	**Not Known** (cannot be estimated 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 reaction* 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 maculo-papular Urticaria		toxic epidermal necrolysis (TEN)*, Stevens Johnson syndrome (SJS)*, drug reac with eosinophilia and syste symptoms (DRESS)*, acute generalized exanthematous pustulosis (AGEP*, angioedema*, dermatitis exfoliative*, dermatitis bullous*, erythema multiforme*, pruritus, rash morbilliform*
Musculoskeletal Disorders				polyarthritis
Investigations	liver function test abnormal			
Renal and urinary disorders				Acute kidney injury#

* ADR identified post-marketing.

‡ ADRs apply only to oral

formulations. # See section 4.4.

Diarrhoea occurs in up to 20% of patients; it may commence during treatment or may be delayed until sometime after therapy has been completed. This may progress to colitis, including pseudomembraneous colitis (see section 4.4), which may have life-threatening complications. Fatalities have been reported.

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: 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.

Features: Antibiotics cause very little effect when taken in acute overdosage. There may be nausea and vomiting. Skin rashes may occur if the patient is already allergic to the antibiotic.

Management: The serum biological half-life of clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis. Hemodialysis and peritoneal dialysis are not effective in removing clindamycin from the serum.

Gastric decontamination is not necessary. Give oral fluids for severe vomiting and diarrhoea if required. Other measures should be taken as indicated by the patient's clinical condition. 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: Lincosamides

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. Most Gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin. 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.

Mechanism of resistance

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

Breakpoints

The following MICs have been proposed to separate susceptible from intermediately susceptible and resistant organisms.

Susceptible: ≤ 1.6 μg/ml

Intermediate: >1.6 - ≤ 4.8 μg/ml

Resistant: > 4.8 μg/ml

The minimum inhibitory concentrations (MIC) breakpoints are as follows:

Eucast

Staphylococci: sensitive ≤ 0.5 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
Streptococcus viridans
Anaerobes
Bacteriodes fragilis group
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.

Resistance:

Resistance to clindamycin usually occurs via macrolide-lincosamide- streptograminB (MLSB) type of resistance, which may be constitutive or inducible. This is mediated by a variety of acquired genes that encode methylases targeted at the peptidyl transferase center of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides (clindamycin and lincomycin) and type B streptogramins, but not to type A streptogramins

5.2 Pharmacokinetic properties

General characteristics of active substance

Absorption

After oral administration clindamycin is absorbed quickly and almost completely (>90%). The absorption is not affected by food but the rate of absorption may be reduced. The peak plasma concentration is achieved within

approximately 45 minutes after oral administration. After doses of 300 and 600 mg peak plasma concentrations of 4 and 8 micrograms per ml, respectively, have been reported. The bioavailability is non-linear and decreases with increasing doses. Following a 600 mg dose the absolute bioavailability is 53±14%.

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 fetal circulation and appears in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Clindamycin is distributed very highly intracellular due to the

lipophilic properties. The intracellular concentrations are 10-50 times higher than the extracellular concentrations. Over 90% of clindamycin in the circulation is bound to plasma proteins. The half-life is 2 to 3 hours, although this may be prolonged in pre-term neonates and patients with severe renal impairment.

Metabolism

Clindamycin undergoes metabolism, presumably in the liver, to the active *N-demethyl* and sulphoxide metabolites, and also some inactive metabolites and about 4% in the faeces: the remainder is excreted as inactive metabolites.

Excretion

Half-life is approximately two and a half hour in children and approximately 3 hours in adults. Clindamycin is excreted as biological active and biological inactive metabolites in faeces, urine and bile. Faecal excretion is predominant. About 10% of the drug is excreted in the urine as active drug 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

Elderly:

The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate are not altered by increased age.

Patients with renal impairment:

In the presence of renal impairment, elimination half-life is prolonged; however, a dosage reduction is unnecessary in the event of mild to moderate impairment of renal function.

Patients with hepatic impairment:

In patients with moderate to severe hepatic impairment the half life is prolonged, but when giving the dose every 8 hour accumulation is rarely seen. Dose reduction is normally not necessary in patients with hepatic impairment.

5.3 Preclinical safety data

In dogs, repeated high oral doses produced ulceration of the mucosa of the stomach and gall bladder.

However preclinical data reveal no special hazard for humans based on studies of repeat dose toxicity, or effects on male and female fertility as well as embryo fetal and postnatal development, genotoxicity.

Carcinogenicity studies have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised starch
Purified talc
Magnesium stearate

The capsule shells contain
Gelatin
Purified water
Indigotine (E132)
Titanium dioxide (E171)
Erythrosine (E127)

Edible black printing ink contains (TekPrint™ SW-9008 Black Ink): Shellac
Propylene glycol (E1520)
Black iron oxide (E172)
Potassium hydroxide (E525)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVdC film and Aluminium foil. Pack sizes 30, 60, 90 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Strandhaven Ltd t/a Somex Pharma
Ilford, Essex
IG3 8BS .UK

8 MARKETING AUTHORISATION NUMBER(S)

PL15764/0126

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/09/2019

10 DATE OF REVISION OF THE TEXT

01/11/2023