SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clindamycin 75 mg Capsules, Hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 75mg of clindamycin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

capsule, hard

Green transparent (body) / Green transparent (Cap), size ‘3’ hard gelatin capsule printed with ‘M’ on cap and ‘40’ on body filled with white to off-white granular powder. Approximately 16 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antibacterial. Serious infections caused by susceptible Gram-positive organisms, 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.

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

4.2 Posology and method of administration

Posology
Adults:
Moderately severe infection, 150-300 mg every six hours; severe infection, 300-450 mg every six hours.

Elderly patients:
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.

Paediatric population:

Clindamycin hydrochloride capsules should only be used for children who are able to swallow capsules.

Clindamycin should be dosed based on total body weight regardless of obesity.

Doses of 12-25 mg/kg/day six hourly depending on the severity of the infection.

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 /Hepatic Impairment: Clindamycin dosage modification is not necessary in patients with renal or hepatic insufficiency.

Note: In cases of beta-haemolytic streptococcal infection, treatment with Clindamycin should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

Method of administration
Oral. Clindamycin Capsules should always be swallowed whole and washed down with a full glass of water while in an upright position and no less than 30 minutes before lying down to avoid the possibility of oesophageal irritation. Absorption of Clindamycin is not appreciably modified by the presence of food.

4.3 Contraindications

Clindamycin capsules is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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).

Clindamycin capsules should only be used in the treatment of serious infections. In considering the use of the product, the practitioner should bear in mind the type of infection and the potential hazard of the diarrhoea which may develop, since cases of colitis have been reported during, or even two or three weeks following, the administration of clindamycin.

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 diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhea 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Due to the risk of oesophagitis and oesophageal ulcer, it is important to ensure compliance with administration guidance (see Sections 4.2 and 4.8)

If therapy is prolonged, liver and kidney functions 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).

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.

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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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 may enhance the action of other neuromuscular blocking agents. Therefore, it should be used with caution in patients receiving such agents.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, has 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.

Breast-feeding
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	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 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		Abdominal pain, Diarrhoea	Nausea, Vomiting			Oesophageal Ulcer *‡≠, Oesophagitis *‡≠

Hepatobiliary Disorders						Jaundice*
Skin and Subcutaneous Tissue Disorders			Rash maculopa pular Urticaria			Toxic epidermal necrolysis (TEN)*, Stevens-Johnson Syndrome (SJS)*, Drug reaction with eosinophilia And systemic symptoms (DRESS)*, Acute generalised exanthematous pustulosis (AGEP) *, angioedema*, Erythema Multiforme, Dermatitis exfoliative*, Dermatitis bullous*, Rash morbilliform, Pruritus
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.
≠ Possible occurrence of oesophagitis and oesophageal ulcer, particularly if taken in a lying position and/or with a small amount of water.

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.

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: Lincosamide 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.

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

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

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).

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 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 sulphoxide 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

None stated

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Talc
Magnesium stearate

Capsule shell:
Gelatin
FD&C Blue 1 (E133)
D&C Yellow 10 (E104)

Printing ink:
Shellac
Potassium hydroxide
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister: 36 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Clindamycin Capsules 75 mg is available in blister packs (aluminium foil/PVC) of 6, 10, 12, 24, 30 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Brown & Burk UK Limited,
5 Marryat Close,
Hounslow,
TW4 5DQ,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

PL 25298/0064

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/11/2017 / 04/02/2025

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