Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 150 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
Turquoise blue opaque/ green, hard gelatin capsule printed with **'R/CLM 150'** in black on both cap and body.
The capsule contains white to off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clindamycin is indicated when infections caused by susceptible micro-organisms are severe and recurrent and not responding to first line antibiotics and as an alternative treatment in the case of penicillin-allergic patients with infections caused by Gram-positive aerobic bacteria. The infections include:

- Infections of respiratory tract.
- Skin and soft tissue infections.
- Bone and joint infections.
- Female pelvic and genital infections.
- Intra-abdominal infections.
- Severe infections (except cerebrospinal infections) caused by Gram-positive microorganisms (except *Enterococcus faecalis*), in particular Staphylococci spp, penicillin sensitive Streptococcus and pneumoniae strains.

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

4.2 Posology and method of administration

Oral.
Capsules should be swallowed with a glass of water.

Adults, adolescents over 12 years of age and the elderly:
The usual dose is 150 – 450 mg every six hours.

Children: The usual dose is 3 - 6 mg/kg every six hours. The dose can be increased or decreased depending on the severity of infections (not to exceed the adult dose). Dose range 8-20 mg/kg/day in 3 or 4 divided doses.

The dose and method of administration is determined by the severity and sensitivity of the causative organism(s) and the condition of the patient like for all antibiotics, in severe infections, *in vitro* sensitivity tests should be conducted.

Alternative formulations of clindamycin are available for treating children for whom the capsules are unsuitable or for doses that cannot be reached by this pharmaceutical form. In case of severe clinical status IV therapy is preferred to oral therapy.

In cases of Beta- Haemolytic streptococcal infections, treatment with clindamycin capsules should continue for at least 10 days to diminish the likelihood of subsequent rheumatic fever or glomerulonephritis.

The duration of treatment depends on the clinical response of the patient. However, due to the risk of severe disruption of the faecal flora and its consequences (see sections 4.4), treatment should be kept to the minimum. If prolonged therapy is considered to be unavoidable, the patient should be carefully monitored for adverse effects (see section 4.4).

4.3 Contraindications

Known hypersensitivity to clindamycin or lincomycin or to any of the excipients.

4.4 Special warnings and precautions for use

Colitis: Clindamycin therapy has been associated with severe colitis which may be fatal also some severe and persistent cases of diarrhoea have been reported during clindamycin treatment or after it. Sometime blood and mucus have been found in the faeces in connection with the diarrhoea, and acute colitis has sometimes resulted from the diarrhoea. Care should be taken when prescribing clindamycin to a patient who has a tendency towards gastrointestinal illnesses, in particular colitis. Drugs which cause intestinal block should be avoided.

The most commonly implicated cause is an overgrowth of toxin producing *Clostridium difficile* as a result of disruption of the bowel flora by clindamycin. If marked diarrhoea occurs during therapy, clindamycin should be discontinued immediately and appropriate diagnostic and therapeutic measures should be instituted.

Lactose intolerance: Clindamycin capsules contain inactive ingredients including lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Hepatic and renal insufficiency: In severe renal impairment, peak plasma levels of clindamycin may be up to three times normal and the elimination half-life is prolonged. Dose reduction and/or an increased dose interval should be considered. In moderate and severe degrees of hepatic impairment, peak plasma levels of clindamycin are higher than normal and the elimination half-life is prolonged. Dose reduction and/or an increased dose interval should be considered.

Serum clindamycin levels should be estimated. Laboratory tests for renal and hepatic function should be carried out during prolonged therapy.

Superinfection particularly with Candida is possible. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Clindamycin is not used for the treatment of susceptible strains causing meningeal infections as it is not sufficiently secreted into the cerebrospinal fluid.

Clindamycin should not be given in patients with acute viral infections of the respiratory tract.

Clindamycin should be reserved for serious infections, where less toxic antibiotics are considered inappropriate.

Hypersensitivity: Clindamycin should be used with caution in patients sensitive to other antibiotics.

4.5 Interaction with other medicinal products and other forms of interaction

Antagonism has been demonstrated between clindamycin and erythromycin *in vitro*. Because there is a possibility of a clinically significant interaction, clindamycin should not be given in combination with macrolides or streptogramin antibacterial agents.

Clindamycin has been found to have properties affecting the neuromuscular block which may increase the effect of

other substances causing neuromuscular block. Therefore the drug should be used with caution in patients receiving this kind of medication as unexpected life-threatening events may occur in the course of surgery.

The infectious and inflammatory context, age and the general status of the patient appear as risk factors. In these circumstances, it is difficult to know the relationship between the infectious disease and its treatment in the occurrence of INR disorders. However, some classes of antibiotics are more implicated, notably fluoroquinolones, macrolides, cyclines, cotrimoxazole and some cephalosporins.

4.6 Pregnancy and lactation

Pregnancy:
The drug crosses the placenta. The safety of use during pregnancy and for the neonate has not been established.

A larger-scale study with pregnant women in which approximately 650 neonates exposed to clindamycin during the first trimester of pregnancy were examined, did not reveal an elevated abnormality rate. In animal studies clindamycin was not teratogenic (see also 5.3 preclinical data).

The concentration of clindamycin in the cord blood was found to be approximately 50% of the maternal serum concentration. It is assumed that a concentration with a therapeutic effect can be reached in the foetus. During pregnancy Clindamycin should only be used after a risk/benefit assessment.

Lactation:
During lactation Clindamycin should only be used after a risk/benefit assessment. Passage into the breast milk has been demonstrated. Apart from one single case study there have been no reports of any undesirable effects on breast-fed infants.

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 sensitisation should be borne in mind.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that clindamycin has any effect on the ability to drive and/or use machines.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with clindamycin and other macrolide antibiotics with the following frequencies: very common (≥10%), common (≥1.0% - <10%), uncommon (≥0.1% -< 1%), rare (≥0.01 – <0.1%) and very rare (<0.01%) including isolated reports.

Immune system disorders
Uncommon (≥0.1% -< 1%): skin rash and urticaria. In wider areas slight or moderate skin rash resembling measles or symptoms resembling Stevens-Johnson syndrome can occur.

Rare (≥0.01 – <0.1%): anaphylactic reactions.

Nervous system disorders
Uncommon (≥0.1% -< 1%): Neuromuscular blocking activity.

Blood and lymphatic system disorders
Rare (≥0.01 – <0.1%): transient neutropenia (leucopenia) and agranulocytosis, and thrombocytopenia have been reported.

Gastrointestinal disorders
Common (≥1.0% - <10%)(> 1%): stomach aches, nausea, vomiting and diarrhoea (see Special warning and precautions for use) and irritation of the gastric tract can occur.

Rare (≥0.01 – <0.1%): oesophagitis occur.

Hepato-biliary disorders
Rare (≥0.01 – <0.1%): jaundice and changes in the liver functions (also in levels of serum transaminases) tests have been observed.

Skin and subcutaneous tissue disorders
Uncommon (≥0.1% -< 1%) pruritus, skin rash, urticarias have occurred.
Rare (≥0.01 – <0.1%) exfoliative dermatitis and vesiculobullous eruptions can occur.

Musculoskeletal
Rare (≥0.01 – <0.1%): Polyarthritis.

Reproductive system and breast disorders
Common (≥1.0% - <10%): observed side effect is vaginitis.

General disorders and administration site conditions.

4.9 Overdose

In cases of overdosage, no specific treatment is indicated.

The serum biological half-life of clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: JO1FF01.
Pharmacotherapeutic group: Macrolides and lincosamides.

Mode of action
The antibacterial spectrum of Clindamycin Hydrochloride includes a wide range of anaerobic bacteria and gram-positive aerobic bacteria. Clindamycin is a semi-synthetic antibiotic which is obtained from lincomycin by replacing 7 (R)-hydroxyl group with 7(S)-chloro substituent. 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.

Breakpoints
The following MIC breakpoints, separating susceptible from intermediately susceptible and intermediately susceptible from resistant organisms are suggested for other than streptococci (NCCLS, 1993):
Susceptible (S) ≤0.5 mg/L.
Resistant (R) ≥ 4.0 mg/L.

For streptococci the breakpoints are:

Susceptible (S) ≤ 0.25 mg/L.
Resistant (R) ≥ 1.0 mg/L.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe infections. This information gives only approximate guidance

on probabilities whether microorganisms will be susceptible to this antibiotic. Where resistance patterns for particular species are known to vary within the European Union, this is shown below as (*):

Antibacterial Spectrum	**Percentage range of resistance**
The following bacteria are susceptible or intermediately susceptible:	
Bacteroides fragilis group	***< 10***
Clostridium perfringens	***0.06***
Chlamydia trachomatis	***1 - 2***
Coryneforms, aerobic	***0***
Legionella species	***< 50***
Staphylococcus aureus (OS)	***< 10***
S. aureus	***0 – 29.2***
S. aureus (MR)	***26-28.21***
Staphylococcus epidermidis	***10***
S. epidermidis (OS)	***< 10***
S. epidermidis (MR SP)	***12***
S. epidermidis (NSP)	***12***
Staphylococcus saprophyticus	***< 10***
Staphylococci (MR)	***40.8 (70 - 80 %)****
Streptococcus agalactiae	***0-<10***
Streptococcus bovis	***>10, <50***
Streptococcus pneumoniae	***0-1.4 (35 - 70 %)****
Streptococcus pyogenes	***0***
Streptococci, β- haemolytic (Gp C,F,G)	***0-< 10***
Streptococci, viridans Gp	***0-< 10***
The following are resistant:	
clostridium difficile	***80.3***
Corynebacterium urealyticum	***> 50***
Coryneforms, aerobic (MLSR)	***100***
Enterococcus faecium	***> 50***
Enterococcus faecalis	***> 50***
Legionella pneumophillia	***> 50***

OS: Oxacillin susceptible.
MR: methicillin resistant.
MS: methicillin susceptible.
ES: erythromycin susceptible.
ER: erythromycin resistant.
MLSR: macrolide-lincosamide-streptogramin type B resistant.
cMLSR: constitutive macrolide-lincosamide-streptogramin type B resistant.
SP: slime producing.
NSP: non-slime producing.

Clindamycin has an *in-vitro* and *in-vivo* activity on *Toxoplasma gondii*.

All isolates of *Enterococcus faecalis* are resistant to clindamycin.

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 clindamycin should not be used

while awaiting susceptibility test results if there is any suspicion of MRSA.

Complete cross resistance among lincosamides, erythromycin, azithromycin and other macrolides for *S.pneumoniae*, beta-haemolytic streptococcus of group A, *E .faecalis* and *S .aureus*, including methicillin resistant *S .aureus* (MRSA).

Mechanism of Resistance
When tested by *in vitro* methods, some staphylococcal strains originally resistant to erythromycin rapidly developed resistance to clindamycin. The mechanisms for resistance are the same as for erythromycin, namely methylation of the ribosomal binding site, chromosomal mutation of the ribosomal protein and in a few staphylococcal isolates enzymatic inactivation by a plasmid-mediated adenyltransferase.

5.2 Pharmacokinetic properties

About 90% of a dose of clindamycin hydrochloride is absorbed from the gastro-intestinal tract. Plasma concentrations of 2 to 3 mg/L occur within one hour after a 150 mg dose of clindamycin. 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 cerebrospinal fluid in significant concentrations, the mean volume of distribution is 1.1 L/kg. 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. About 40 – 90% of clindamycin in the circulation is bound to plasma proteins.

Clindamycin undergoes metabolism, presumably in the liver, to the active N-demethyl and sulphoxide metabolites and also some inactive metabolites. The plasma elimination half-life is 2 to 3 hours, although this may be prolonged in neonates, especially when premature, and in patients with moderate or severe degrees of renal or hepatic impairment. About 10% of the drug is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Clindamycin is not effectively removed from the blood by haemodialysis or peritoneal dialysis.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of repeat dose toxicity, reproductive toxicity or genotoxicity. Carcinogenicity studies have not been conducted. In dogs, repeated high oral doses produced ulceration of the mucosa of the stomach and gall bladder.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Lactose monohydrate
Maize starch
Talc
Magnesium stearate

Capsule shell:
Quinoline Yellow (E104)
Brilliant Blue (E133)
Titanium dioxide (E171)
Gelatin

Printing ink:
Shellac Ph.Eur.
Propylene glycol
Black iron oxide (E 172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

4, 12, 16, 20, 24, 30, 32, 40, 60, or 100 capsules in aluminium/PVC/PVDC blister pack.
100 capsules in HDPE plastic bottles with a polypropylene safety cap.
100 capsules in HDPE plastic bottles with a polypropylene screw cap
Not all pack sizes will be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy Ireland Limited
Spafield
Cork Road
Cashel
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 408/60/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 March 2006

10 DATE OF REVISION OF THE TEXT