Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 150 mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains clindamycin phosphate equivalent to 150 mg clindamycin

Each 2 ml ampoule contains 300 mg clindamycin

Each 4 ml ampoule contains 600 mg clindamycin

Excipients: sodium 6.57 mg per ml (prior to dilution)

For a full list excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion

Product imported from the UK:
Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clindamycin is indicated for the treatment of severe infections (see section 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

Parenteral (IM or IV administration). Clindamycin 150 mg/ml Solution for Injection and Infusion **must** be diluted prior to I.V. administration and should be infused over at least 10-60 minutes.

Adults: Serious infections: 600 mg-1.2 g/day in two, three or four equal doses.

More severe infections: 1.2-2.7 g/day in two, three or four equal doses.

Single I.M. injections of greater than 600 mg are not recommended nor is administration of more than 1.2 g in a single one-hour infusion.

For more serious infections, these doses may have to be increased. In life-threatening situations, doses as high as 4.8 g daily have been given intravenously to adults.

Alternatively, the drug may be administered in the form of a single rapid infusion of the first dose followed by continuous IV infusion.

Children (over 1 month of age): Serious infections: 15-25 mg/kg/day in three or four equal doses.

More severe infections: 25-40 mg/kg/day in three or four equal doses. In severe infections it is recommended that children be given no less than 300 mg/day regardless of body weight.

Elderly patients: The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate 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 should not be influenced, therefore, by age alone.

Dosage in renal/hepatic impairment: clindamycin dosage modification is not necessary in patients with renal or hepatic insufficiency

Treatment for infections caused by beta-haemolytic streptococci should be continued for at least 10 days to guard against subsequent rheumatic fever or glomerulonephritis.

The concentration of clindamycin in diluent for infusion should not exceed 18 mg per ml and INFUSION RATES SHOULD NOT EXCEED 30 MG PER MINUTE. The usual infusion rates are as follows:

Dose	Diluent	Time
300 mg	50 ml	10 min
600 mg	50 ml	20 min
900 mg	50-100 ml	30 min
1200 mg	100 ml	40 min

4.3 Contraindications

Clindamycin 150 mg/ml Solution for Injection and Infusion is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings
Clindamycin 150mg/ml Solution for Injection and Infusion 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 125mg to 500mg 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 *C. 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 150mg/ml Solution for Injection and Infusion to individuals with a history of gastro-intestinal disease, especially colitis.

Periodic liver and kidney function and haematology tests should be carried out during prolonged therapy. Such monitoring is also recommended in neonates and infants. Safety and appropriate dosage in infants less than one month old have not been established.

Prolonged administration of Clindamycin 150mg/ml Solution for Injection and Infusion, as with any anti-infective, may result in super-infection due to organisms resistant to clindamycin. The use of Clindamycin 150 mg/ml solution for injection and infusion may result in the overgrowth of non-susceptible organisms particularly yeasts.

Care should be observed in the use of Clindamycin 150mg/ml Solution for Injection and Infusion in atopic individuals, particularly those with asthma.

Since Clindamycin 150mg/ml solution for injection and infusion does not diffuse adequately into cerebrospinal fluid, the drug should not be used in the treatment of meningitis.

Antibiotics can reduce the efficacy of the combined oral contraceptive pill. Additional contraceptive precautions should be taken during treatment and for up to seven days after stopping treatment.

This medicinal product contains 0.286mMol (or 6.57mg) sodium per ml of solution (prior to dilution). To be taken into consideration by patients on a controlled sodium diet.

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.

4.6 Fertility, pregnancy and lactation

Safety for use in pregnancy has not been established. Animal studies do not indicate reproductive toxicity (see section 5.3).

Lactation

Clindamycin is excreted in human milk. Caution should be exercised when Clindamycin 150 mg/ml Solution for Injection and Infusion is administered to a nursing mother. It is unlikely that a nursing infant can absorb a significant amount of clindamycin from its gastro-intestinal tract.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Gastro-intestinal tract: Oesophageal ulcers have been reported as serious adverse events during postmarketing surveillance, and oesophagitis with oral preparations, nausea, vomiting, abdominal pain and diarrhoea (*See Section* 4.4 Special Warnings and Precautions for use: Warning*s*).

Blood and lymphatic system disorders: Transient neutropenia (leucopenia), eosinophilia, agranulocytosis and thrombocytopenia have been reported. No direct aetiological relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Immune system disorders: a few cases of anaphylactic reactions have been reported.

Skin and subcutaneous tissue disorders: Maculopapular rash and urticaria have been observed during drug therapy. Generalised mild to moderate morbilliform-like skin rashes are the most frequently reported reactions. Rare instances of erythema multiforme some resembling Stevens-Johnson syndrome, have been associated with clindamycin. Pruritus, vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported. Serious cutaneous adverse reaction (SCAR) and rare cases of toxic epidermal necrolysis have been reported during postmarketing surveillance.

Hepatobiliary disorders: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Cardiac disorders: Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration. (See Section 4.2 Posology and method of administration)

Nervous system disorders: Frequently, cases of dysgeusia have been observed upon systemic administration of clindamycin using injectables (IM and IV), capsules or oral granulate solutions, which include a few (non-frequent) serious adverse events.

General disorders and administration site conditions: Local irritation, pain, abscess formation have been seen with IM injection. These reactions can be minimised by deep IM injection and avoiding the use of an indwelling catheter.

Thrombophlebitis has been reported with IV injection.

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.

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: J01 FF01

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 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 (MLS_B) type of resistance, which may be constitutive or inducible.

Breakpoints

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: sensitive ≤ 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 pneumoniae
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.

5.2 Pharmacokinetic properties

General characteristics of active substance

Following parenteral administration, the biologically inactive clindamycin phosphate is hydrolysed to clindamycin. When the equivalent of 300 mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 microgram/ml is achieved within three hours; 600 mg gives a peak concentration of 9 microgram/ml. In children, peak concentration may be reached within one hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms per ml respectively are achieved by the end of infusion.

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 foetal circulation and appears 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. 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, to the active *N*-demethyl and sulphoxide metabolites and also some inactive metabolites. 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. 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.

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

Disodium edetate
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Solutions of clindamycin salts have a low pH and incompatibilities may reasonably be expected with alkaline preparations or drugs unstable at low pH. Incompatibility has been reported with: ampicillin sodium, aminophylline, barbiturates, calcium gluconate, ceftriaxone sodium, ciprofloxacin, diphenylhydantoin, idarubicin hydrochloride, magnesium sulphate, phenytoin sodium and ranitidine hydrochloride.
This medicinal product must not be mixed with other medicinal products except those mentioned in sections 6.6.

6.3 Shelf life

Unopened:The shelf life expiry date of this product should be the date shown on the ampoule and outer packaging of the product on the market in the country of origin.
After dilution: 24 hours
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2 to 8^{o}C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C. Keep ampoules in the outer carton.
Do not refrigerate or freeze.
Please refer to Sections 6.3 and 6.6 for storage after dilution.

6.5 Nature and contents of container

Cardboard outer carton containing glass ampoules.
Pack size: 5 x 2 ml
5 x 4 ml

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

Any unused product or waste material should be disposed of in accordance with local requirements.
Solution for injection is for single use only. Any unused product should be discarded.
Infusion: Clindamycin 150 mg/ml Solution for Injection and Infusion has been shown to be physically and chemically compatible for at least 24 hours in dextrose 5% water and sodium chloride injection solutions containing the following antibiotics in usually administered concentrations: Amikacin sulphate, aztreonam, cefotaxime sodium, ceftazidime sodium, gentamicin sulphate, piperacillin and tobramycin.

The compatibility and duration of stability of drug admixtures will vary depending upon concentration and other conditions The reconstitution/dilution should be made under aseptic conditions. The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/156/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd February 2012

10 DATE OF REVISION OF THE TEXT

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