CLINDAMYCIN 150MG/ML SOLUTION FOR INJECTION

PL 24780/0002

UKPAR

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CLINDAMYCIN 150MG/ML SOLUTION FOR INJECTION

PL 24780/0002

LAY SUMMARY

The MHRA granted Villerton Invest SA a Marketing Authorisation (licence) for the medicinal product Clindamycin 150mg/ml Solution for Injection (PL 24780/0002). This is a prescription-only medicine (POM).

Clindamycin contains the active substance clindamycin phosphate, which is one of a group of medicines called antibiotics. These are used to kill the bacteria or germs that cause infections.

Clindamycin is usually reserved for the treatment of serious infections, especially when other antibiotics have been unable to clear infection and when the infection is caused by bacteria that are sensitive to clindamycin.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Clindamycin 150mg/ml Solution for Injection outweigh the risks, hence a marketing Authorisation has been granted.

CLINDAMYCIN 150MG/ML SOLUTION FOR INJECTION

PL 24780/0002

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisation for the medicinal product Clindamycin 150mg/ml Solution for Injection (PL 24780/0002) to Villerton Invest SA on 6th February 2008. The product is a prescription-only medicine.

This application was submitted as an abridged application according to Article 10(1) of Directive 2001/83/EC, claiming to be a generic medicinal product of the original product Dalacin C Phosphate Sterile Solution manufactured by Pharmacia Limited, PL 00032/0042 which was first authorised in December 1990.

Clindamycin is an antibacterial used for 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 such as *Bacteroides* spp, *Fusobacterium* spp, *Propionibacterium* spp, *Peptostreptococcus* spp. and microaerophilic streptococci.

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

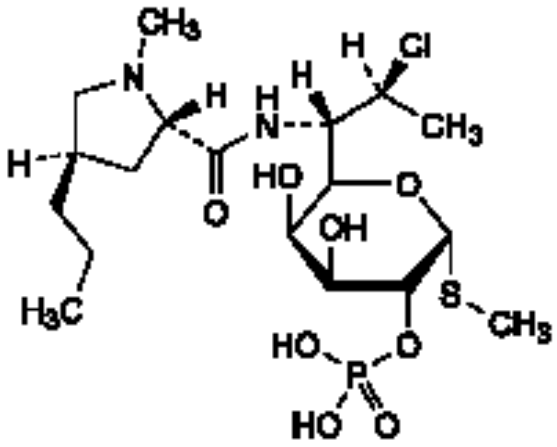
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Clindamycin Phosphate

Structure



Molecular formula: $C_{18}H_{34}ClN_2O_8PS$

Molecular weight: 505.00

Clindamycin phosphate is a white or almost white powder, slightly hygroscopic, freely soluble in water, very slightly soluble in alcohol, practically insoluble in methylene chloride. It shows polymorphism.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Clindamycin phosphate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated supporting a retest period of 2 years when stored in a container comprised of a low density polyethylene bag in a high density polyethylene bottle.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely edetate disodium, sodium hydroxide and water for injections. All excipients used comply with their respective European Pharmacopoeial monographs.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients. No materials of animal or human origin are contained in or used in the manufacture of this product. No genetically modified organisms are included in this product.

No overages are used.

Impurity profiles

Impurity profiles for the drug product were found to be similar to that of the reference product.

Manufacture

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is packaged in Type I glass ampoules. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging complies with EU legislation regarding contact with solutions for parenteral and ophthalmic use Directive 2002/72/EC (as amended). The product is packaged in sizes of 2ml or 4ml ampoules.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set with the storage precautions: Do not store above 25ºC. Do not refrigerate or freeze.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion

It is recommended that Marketing Authorisation is granted for this application.

The proposed product is considered to be generic medicinal product to the reference product with respect to qualitative and quantitative content of the active substance and pharmaceutical form. It was not necessary to demonstrate bioequivalence.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION

This national application was made in the United Kingdom under EU Directive 2001/83/EC as amended, Article 10(1) generic application for marketing authorisation for Clindamycin Injection 150mg/ml, solution for injection. This product is a generic medicinal product of Dalacin C Phosphate Sterile Solution. Dalacin C Phosphate Sterile Solution was authorised in the UK in 1990. The current licence PL 00032/0042 is held by Pharmacia Ltd.

CLINICAL BACKGROUND

Clindamycin is a semi-synthetic antibiotic derived from lincomycin and belongs to the group of lincosamides. Clindamycin is mainly bacteriostatic but it may be bactericidal depending on its concentration at the site of infection and on the susceptibility of the pathogen.

The spectrum of activity of clindamycin covers most gram-positive aerobes and anaerobes. It is also active against many gram-negative anaerobes and some protozoa.

Most (>90%) methicillin-resistant S. aureus (MRSA) are resistant to clindamycin. Up to 50% of MRSA are reported to be resistant in the USA.

The clinical use of systemic clindamycin is limited by its association with C. difficile enterocolitis. The agent can disrupt faecal flora but does not inactivate C. difficile. Antibiotic-associated diarrhoea, colitis and sometimes pseudomembraneous colitis may result from the use of clindamycin.

Clindamycin would not usually be used unless alternative agents had been ruled out. There are few cases in which the susceptibility of the pathogenic organism(s) and host-limiting factors would require the use of clindamycin.

INDICATIONS

The following indications are taken from the submitted SPC:

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 such as *Bacteroides* spp, *Fusobacterium* spp, *Propionibacterium* spp, *Peptostreptococcus* spp. and microaerophilic streptococci.
Clindamycin does not penetrate the blood/brain barrier in therapeutically effective quantities.

DOSE & DOSE SCHEDULE

The dose advice is fully in line with the SPC for the UK reference product:

CLINICAL PHARMACOLOGY
Pharmacokinetics

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

Over 90% of clindamycin is bound to protein. There is high penetration of most tissues and bones but clindamycin does not reach the cerebrospinal fluid in significant concentrations. High concentrations occur in bile. Clindamycin accumulates in leucocytes and macrophages.

Clindamycin diffuses across the placenta into the fetal circulation and also appears in breast milk.

Metabolism
Clindamycin is extensively metabolised, mostly in liver, by N-demethylation, sulphoxidation and hydrolysis. Some of the metabolites are microbiologically active.

Excretion
Clindamycin has a short plasma elimination half-life (about 2.5 h; extended to up to 4.5 h in the elderly and in renal failure). It is excreted mainly via bile into faeces. About 10% is excreted as the active form, the remainder as inactive metabolites. The elimination half-life is longer in children under 4 weeks of age (and may be over 8 hours in the premature baby). The rate of elimination increases towards adult rates thereafter. The elimination half-life is also increased in patients with severe renal impairment.

Significant accumulation in plasma does not occur after administration of multiple doses.

The drug is not removed by haemodialysis or CAPD.

Impaired renal and hepatic function
The elimination half-life is also increased in patients with severe renal impairment. Elimination is slow in severe hepatic impairment but no dose recommendations can be found.

Special pharmacokinetic considerations in target population -children
The peak concentration of clindamycin may be reached within one hour of the intramuscular injection in children.

Bioequivalence
This application is for a solution for injection. There is no need for a bioequivalence study in accord with the "Note for Guidance on the investigation of bioavailability and bioequivalence".

Pharmacodynamics
The pharmacodynamics of clindamycin is a function of its antibacterial activity. New data are not presented and this is acceptable.

EFFICACY
No new data are submitted and none are required for this type of application.

SAFETY
No new data are submitted and none are required for this type of application.

EXPERT REPORTS
A satisfactory expert report is provided by an appropriately qualified individual.

PATIENT INFORMATION LEAFLET (PIL)
The PIL is satisfactory.

LABELLING
The labelling is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is fully in line with that for the reference product.

DISCUSSION
The SPC, PIL and labelling are fully in line with that for the reference product. A bioequivalence study is not required.

CONCLUSION
There are no medical objections to the granting of a product licence for this preparation.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Clindamycin 150mg/ml Solution for Injection are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for application of this type.

EFFICACY

No new data were submitted and none are required for application of this type.

The SPC, PIL and labelling are satisfactory and consistent with that for reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Clindamycin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

CLINDAMYCIN 150MG/ML SOLUTION FOR INJECTION

PL 24780/0002

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 9th March 2006
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 22nd March 2006
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 4th September 2006, 23rd March 2007, and clinical dossier on 26th February 2007, 1st August 2007,
4	The applicant responded to the MHRA's requests, providing further information on 6th January 2007, 5th July 2007, 16th July 2007, 27th July 2007, 23rd November 2007
5	The applications were determined on 6th February 2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 150mg/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.

Clear, colourless, sterile solution.

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 such as *Bacteroides* spp, *Fusobacterium* spp, *Propionibacterium* spp, *Peptostreptococcus* spp. and microaerophilic streptococci.

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents including national and local guidelines

4.2 Posology and method of administration

Routes of administration:

Intramuscular injection

Intravenous infusion

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.

Renal and/or hepatic insufficiency

The dosage may require reduction in patients with renal and/or hepatic insufficiency due to prolongation of the serum half life.

Children (over 1 month of age):

Serious infections: 15 - 25 mg/kg bodyweight/day in three or four equal doses.

More severe infections: 25 - 40 mg/kg bodyweight/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. See section 4.4. for other factors which should be taken into consideration.

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

Method of administration

Parenteral (intramuscular or intravenous administration). Clindamycin injection **must** be diluted prior to intravenous administration and should be infused over at least 10 – 60 minutes. The minimum time over which infusion should take place depends upon the amount of injection being administered. See following table.

The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL and **infusion rates should not exceed 30mg 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 Injection is contra-indicated in patients previously found to be sensitive to clindamycin, lincomycin or to any component of the formulation.

4.4 Special warnings and precautions for use

Warnings

Clindamycin Injection 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 *C. difficile* on selective media and assay of the stool specimen for the toxin(s) of *C. difficile*.

Precautions

Caution should be used when prescribing Clindamycin Injection 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 infants. Safety and appropriate dosage in infants less than one month old have not been established.

The dosage of Clindamycin Injection may require reduction in patients with renal or hepatic impairment due to prolongation of the serum half-life.

Prolonged administration of Clindamycin Injection, 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 Injection in atopic individuals.

This medicinal product contains less than 1 mmol sodium (23mg) per ampoule i.e. 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.

4.6 Pregnancy and lactation

Pregnancy
Safety for use in pregnancy has not been established.
Lactation
Clindamycin is excreted in human milk. Caution should be exercised when Clindamycin Injection 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

Adverse events are ranked under the following frequency headings:
Common (≥1/100, <1/10)
Uncommon (≥1/1,000, <1/100)
Rare (≥1/10,000,<1/1,000)
Very rare (<1/10,000)

Blood and the lymphatic system disorders	
Uncommon	Transient neutropenia (leucopenia), eosinophilia, agranulocytosis and thrombocytopenia, although no direct aetiologic relationship to concurrent clindamycin therapy could be made.
Immune system disorders	
Very rare	Anaphylactoid reactions
Cardiac disorders	
Rare	Cardiopulmonary arrest has been reported following too rapid intravenous administration (see section 4.2. for recommended rates of infusion)
Vascular disorders	
Rare	Hypotension following too rapid intravenous administration (see section 4.2. for recommended rates of infusion)
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal pain and diarrhoea (see section 4.4). In most cases, these are mild in nature and disappear during or after completion of treatment.
Hepato-biliary disorders	
Very rare	Jaundice

Skin and subcutaneous tissue disorders	
Rare	Pruritus, urticaria, maculopapular rash and exfoliative and vesiculobullous dermatitis. Generalised mild to moderate morbilliform-like skin rashes
Very rare	Erythema multiforme and Stevens-Johnson syndrome
General disorders and administration site conditions	
Uncommon	Local irritation, pain, abscess formation at the place of injection after intramuscular administration. Thrombophlebitis after intravenous administration. These reactions can be minimised by deep i.m. injection and avoiding the use of an indwelling catheter.
Reproductive system and breast disorders	
Rare	Vaginitis
Investigations	
Common	Abnormalities in liver function tests

4.9 Overdose

In cases of overdosage no specific treatment is indicated.

The serum biological half-life of clindamycin is 2-3 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: 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 the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Mechanisms of resistance

Resistance to Clindamycin usually occurs via macrolide-lincosamide-streptogramin-B 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 centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to no cross-resistance to macrolides (all macrolides when constitutive), lincosamides (clindamycin and lincomycin) and type B streptogramins, but not to type A streptogramins.

Breakpoints

The British Society for Antimicrobial Chemotherapy recommends the following breakpoints for staphylococci and α-haemolytic streptococci: susceptible $\leq$ 0.5 mg/L; resistant $\geq$ 1.0 mg/L.

Susceptibility:

The following table lists organisms according to their inherent susceptibility to clindamycin. 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.

Susceptible species

Gram positive aerobes:
Staphylococcus aureus *
Staphylococcus epidermis
Streptococcus pneumoniae
Streptococcus pyrogens
Streptococcus viridans

Gram positive anaerobes:

Bifidobacterium spp.
Eubacterium spp.
Propionbacterium spp.
Clostridium perfringens
Peptococcus spp.
Peptostreptococcus spp.

Gram negative anaerobes:
Bacteroides fragilis group
Bacteroides melaninogenicus
Fusobacterium spp.
Veillonella spp.

Resistant species:

Gram positive aerobes and anaerobes:
Enterococci
Clostridia spp.

Gram negative anaerobes:
Fusobacterium varium
* 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. Clindamycin should not be used while awaiting susceptibility test results if there is any suspicion of resistance to methicillin.
Consideration should be given to official guidance regarding the appropriate use of antibacterial agents.

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 precautions for use**" for further information.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Edetate Disodium

Sodium hydroxide

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.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

Type 1 uncoloured glass ampoule containing 2 ml or 4ml sterile solution.

Each carton contains 1, 5, 10, 20 or 50 ampoules.

6.6 Special precautions for disposal

Clindamycin Injection has been shown to be physically and chemically compatible for at least 24 hours in 5% dextrose and sodium chloride injection solutions. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2-8°C unless dilution has taken place in controlled and validated aseptic conditions.

The product should not be admixed with other drug products which are chemically or physically unstable at low pH (see section 6.2).

The compatibility and duration of stability of drug admixtures will vary depending upon concentration and other conditions.

7 MARKETING AUTHORISATION HOLDER

Villerton Invest S.A.

1, Allée Scheffer,

L-2520 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)

PL 24780/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/02/2008

10 DATE OF REVISION OF THE TEXT

06/02/2008

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clindamycin 150mg/ml, Solution for Injection

Clindamycin phosphate

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do NOT pass it on to others. It may harm them even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:
1. What Clindamycin Injection is and what it is used for
2. Before you are given Clindamycin Injection
3. How Clindamycin Injection is given
4. Possible side effects
5. How to store Clindamycin Injection
6. Further information

The name of your medicine is **"Clindamycin 150mg/ml, solution for injection"** (referred to as Clindamycin Injection throughout this leaflet).

1. WHAT CLINDAMYCIN INJECTION IS AND WHAT IT IS USED FOR

Your medicine contains the active substance Clindamycin phosphate, which is one of a group of medicines called antibiotics. These are used to kill the bacteria or 'germs' that cause infections. Your doctor has decided to give you Clindamycin Injection because you have an infection.

Clindamycin is usually reserved for the treatment of serious infections, especially when other antibiotics have been unable to clear the infection and when the infection is caused by bacteria that are sensitive to Clindamycin.

2. BEFORE YOU ARE GIVEN CLINDAMYCIN INJECTION

Do not take Clindamycin Injection:
- If you are allergic (hypersensitive) to Clindamycin or Lincomycin
- If you are allergic to any of the other ingredients of Clindamycin injection (see section 6 "Further Information")

If you are unsure, talk to your doctor.

Clindamycin should not be used in new born babies.

Before treatment with Clindamycin injection you should tell your doctor:
- If you develop diarrhoea as this may be a sign of colitis (inflammation of the colon, which is the lower part of your bowel).
- If you have liver or kidney problems. Your doctor may give you a lower dose.

If you are taking this medicine for a long time, you will have regular tests to check that your liver and kidneys are working properly. Your doctor will also perform these tests if this medicine is given to an infant less than 2 years old.

Taking other medicines:
Please tell your doctor if you are taking any of the following medicines as they may interact with Clindamycin and lead to side effects:
- "Neuromuscular blocking agents" (these are "muscle relaxants" used mainly during an operation)
- Erythromycin (an antibiotic used to treat infections).
- Oral contraceptives.

If you are taking oral contraceptives, you should also use barrier protection methods (such as a condom) for at least 7 days after stopping treatment with clindamycin.

Please tell your doctor or pharmacist if you are taking or have recently taken, any other medicines including medicines obtained without a prescription.

Pregnancy and breast-feeding:
If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor before you are given this medicine.

Driving and using machines
You may feel dizzy after being given this medicine. If you are affected, do not drive or use any tools or machines.

Important information about some of the ingredients in Clindamycin injection:
This medicine contains less than 1 mmol (23mg) sodium per ampoule i.e. essentially "sodium free"

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for medical or healthcare professionals only.

Instructions for use and handling:
Do not use Clindamycin injection if you notice any particulate matter in the solution or if there is strong colouration of the solution.
Clindamycin Injection has been shown to be physically and chemically compatible for at least 24 hours in 5% dextrose and sodium chloride injection solutions. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2-8°C unless dilution has taken place in controlled and validated aseptic conditions.

Clindamycin injection must be diluted prior to intravenous administration and should be infused over at least 10 – 60 minutes. The minimum time over which infusion should take place depends upon the amount of injection being administered. See following table.

The concentration of clindamycin in diluent for infusion should not exceed 18 mg per mL and **infusion rates should not exceed 30mg 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

The product should not be admixed with other drug products which are chemically or physically unstable at low pH (see section 6.2 of the Summary of Product Characteristics). The compatibility and duration of stability of drug admixtures will vary depending upon concentration and other conditions.

Storing Clindamycin Injection:
Do not store above 25°C. Do not refrigerate or freeze.

3. HOW CLINDAMYCIN INJECTION IS GIVEN

Clindamycin Injection will usually be given by a doctor or nurse, either directly into a muscle or by an intravenous infusion ('drip').
The correct dose will be decided by your doctor and depends on the type of infection and your weight and age.

Adults:
The usual adult dose is 600mg to 1.2g per day given in two, three or four equal doses either directly into a muscle or by infusion into a vein. Larger doses are sometimes needed for more severe infections.

Children:
For infants and children, the dose is usually based on how much they weigh and is usually between 15mg to 25mg per kilogram weight of the child per day, divided into three or four separate doses. Larger doses are sometimes needed for more severe infections.

Your doctor will decide how long you need to be treated with this medicine. You may need to be treated for at least 10 days.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clindamycin Injection can cause side effects, although not everybody gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. Any sudden swelling of the hands, feet, ankles, or swelling of the face, lips, mouth or throat, which may cause difficulty swallowing or breathing, should be reported to a doctor immediately.

Common side effects (probably affecting fewer than 1 in 10 people)
- nausea (feeling sick), vomiting (being sick), stomach ache and diarrhoea
- abnormal results in blood tests of liver function

Uncommon side effects (probably affecting fewer than 1 in 100 people)
- pain, inflammation, itching or swelling at the site of injection
- reduction in the number of white blood cells which makes infections more likely
- reduction in blood platelets which increases risk of bleeding or bruising

Rare side effects (probably affecting fewer than 1 in 1,000 people)
- inflammation of the vagina
- scaling, itching, and redness of the skin (dermatitis)
- itching (pruritus) and rash

Very rare side effects (probably affecting fewer than 1 in 10,000 people)
- yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)
- serious illness with blistering of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome)
- red patches on the skin, often on the back of the hands and arms (Eythema multiforme)

If the injection is given too quickly, this may lead to low blood pressure and in rare cases to cardiac arrest (heart stops working).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

5. HOW TO STORE CLINDAMYCIN INJECTION

Keep out of the reach and sight of children. Do not use Clindamycin Injection after the expiry date which is printed on the label and carton.
Do not store above 25°C. Do not refrigerate or freeze. Your doctor, pharmacist or nurse will know how to store Clindamycin Injection properly.

6. FURTHER INFORMATION

What Clindamycin Injection contains
- The active substance is Clindamycin phosphate 150mg/ml
- The other ingredients are disodium edetate, sodium hydroxide and water for injections.

What Clindamycin Injection looks like and contents of the pack:
Clindamycin Injection is a clear, colourless solution in an ampoule.
Each 2ml ampoule contains 300mg Clindamycin phosphate. Each 4ml ampoule contains 600mg Clindamycin phosphate.
Each carton contains 1, 5, 10, 20 or 50 ampoules. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Villerton Invest SA, 1, Allée Scheffer, L-2520 Luxembourg

Manufacturer:
Lisapharma S.p.A, Via Licinio 11, 22036 Erba – Como, Italy

This leaflet was last approved in MM/YYYY

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Dosage instructions

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.

Renal and/or hepatic insufficiency
The dosage may require reduction in patients with renal and/or hepatic insufficiency due to prolongation of the serum half life.

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.

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

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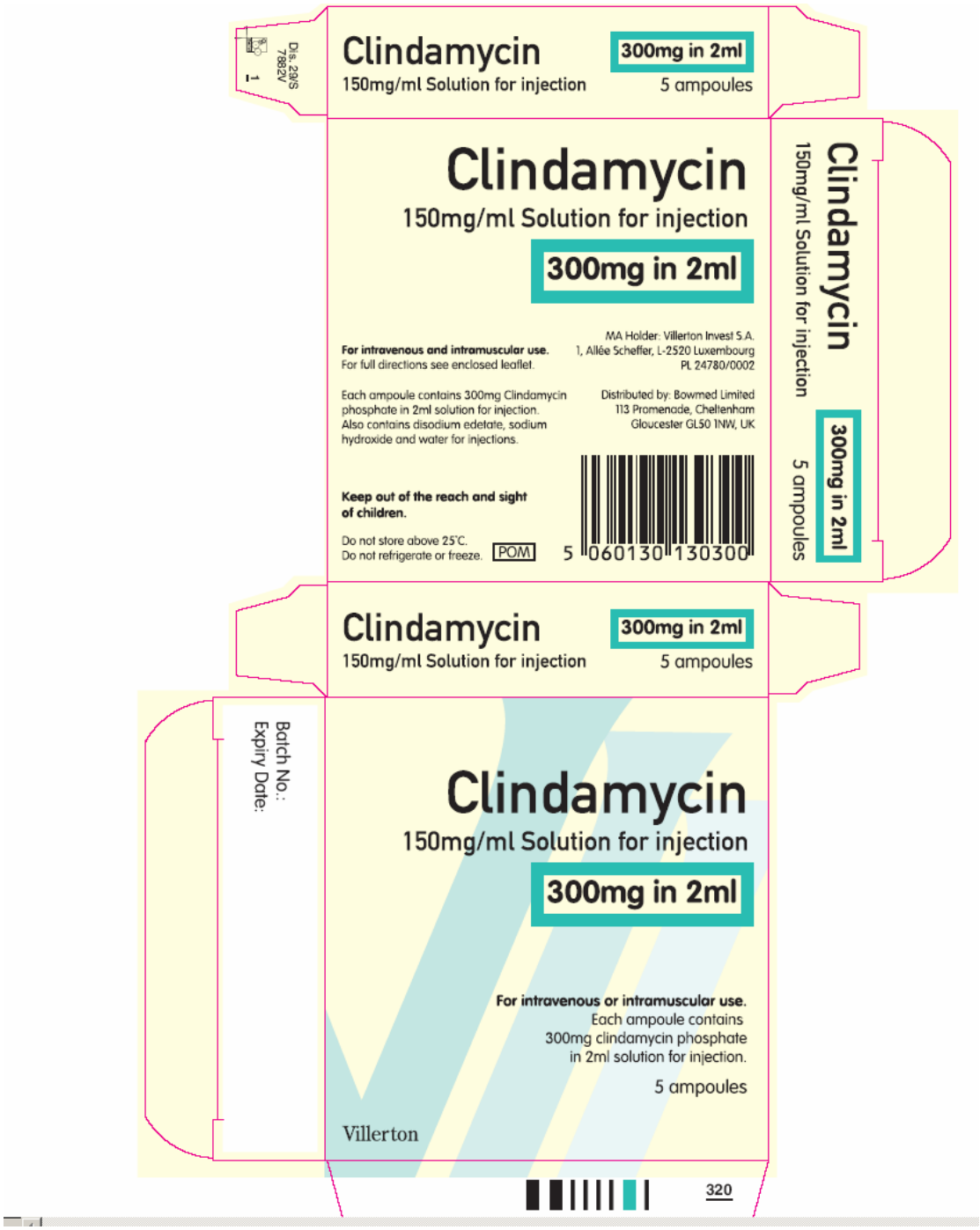
Clindamycin
150mg/ml Solution for injection
300mg in 2ml
5 ampoules
Clindamycin
150mg/ml Solution for injection
300mg in 2ml
For intravenous and intramuscular use.
For full directions see enclosed leaflet.
MA Holder: Villerton Invest S.A.
1, Allée Scheffer, L-2520 Luxembourg
PL 24780/0002
Each ampoule contains 300mg Clindamycin phosphate in 2ml solution for injection.
Also contains disodium edetate, sodium hydroxide and water for injections.
Distributed by: Bowmed Limited
113 Promenade, Cheltenham
Gloucester GL50 1NW, UK
Keep out of the reach and sight of children.
Do not store above 25°C.
Do not refrigerate or freeze.
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Clindamycin
150mg/ml Solution for injection
300mg in 2ml
5 ampoules
Clindamycin
150mg/ml Solution for injection
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Batch No.:
Expiry Date:
Clindamycin
150mg/ml Solution for injection
300mg in 2ml
For intravenous or intramuscular use.
Each ampoule contains
300mg clindamycin phosphate
in 2ml solution for injection.
5 ampoules
Villerton
320


Clindamycin
150mg/ml Solution for injection
600mg in 4ml
For intravenous and intramuscular use.
For full directions see enclosed leaflet.
Each ampoule contains 600mg Clindamycin phosphate in 4ml solution for injection. Also contains disodium edetate, sodium hydroxide and water for injections.
Keep out of the reach and sight of children.
Do not store above 25°C.
Do not refrigerate or freeze.
POM
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PL 24780/0002
Distributed by: Bowmed Limited
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5 060130 130317
Batch No.:
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5 ampoules
Villerton
Clindamycin
150mg/ml Solution for injection
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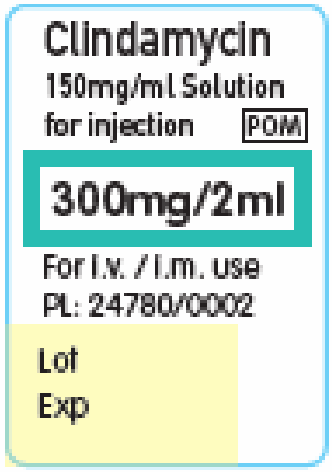
Clindamycin
150mg/ml Solution
for injection
POM
300mg/2ml
For I.v. / I.m. use
PL: 24780/0002
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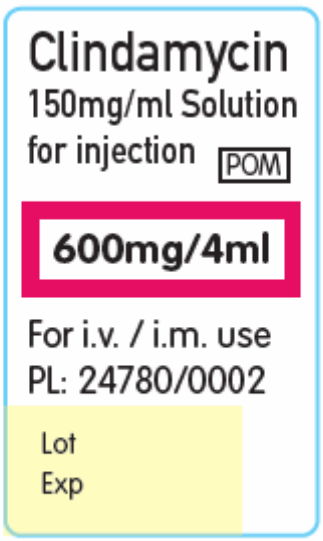
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