Public Assessment Report

Decentralised Procedure

Clindamycin 150mg/ml Solution for Injection or Infusion

Procedure No: UK/H/2220/001/DC

UK Licence No: PL 20046/0072

Focus Pharmaceuticals Ltd
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Clindamycin 150mg/ml Solution for Injection or Infusion (PL 20046/0072; UK/H/2220/001/DC). It explains how the application for Clindamycin 150mg/ml Solution for Injection or Infusion was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Clindamycin 150mg/ml Solution for Injection or Infusion.

For practical information about using Clindamycin 150mg/ml Solution for Injection or Infusion, hard, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Clindamycin Injection’ in this report.

What is Clindamycin Injection and what is it used for?

Clindamycin Injection is a generic medicine’. This means Clindamycin Injection is similar to a ‘reference medicine’ already authorised in the UK called Dalacin C Phosphate Sterile Solution (150mg/ml solution for injection- PL 00032/0042R), which was granted to Pharmacia Limited on 27 December 1990.

Clindamycin Injection is used, usually in hospital, to treat certain serious bacterial infections in adults and children over 1 month old.

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

How does Clindamycin Injection work?

Clindamycin Injection contains the active ingredient, clindamycin (as clindamycin phosphate), which belongs to a group of medicines called antibiotics. These medicines kill bacteria.

How is Clindamycin Injection used?

Clindamycin Injection is available as a solution for Injection or infusion. Clindamycin Injection is administered by a doctor or nurse as an injection into a muscle or as an infusion into a vein (using a drip). The injection or infusion takes 10-60 minutes.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Clindamycin Injection can only be obtained with a prescription.

What benefits of Clindamycin Injection have been shown in studies?

No additional studies were needed as Clindamycin Injection is a generic medicine that is given by injection or infusion and contains the same active substance as the reference medicine, Dalacin C Phosphate Sterile Solution (150mg/ml solution for injection- PL 00032/0042R; Pharmacia Limited).

In addition, the Marketing Authorisation Holder (Focus Pharmaceuticals Limited) has provided data from the published literature on clindamycin.
What are the possible side effects of Clindamycin Injection?
Like all medicines, Clindamycin Injection can cause side effects although not everybody gets them.

For the full list of all side effects reported with Clindamycin Injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Clindamycin Injection.

Why is Clindamycin Injection approved?
It was concluded that, in accordance with EU requirements, Clindamycin Injection have been shown to have comparable quality and to be comparable to Dalacin C Phosphate Sterile Solution (150mg/ml solution for injection- PL 00032/0042R). Therefore, the MHRA decided that, as for Dalacin C Phosphate Sterile Solution (150mg/ml solution for injection- PL 00032/0042R; Pharmacia Limited), the benefits outweigh the identified risks and recommended that Clindamycin Injection can be approved for use.

What measures are being taken to ensure the safe and effective use of Clindamycin Injection?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Clindamycin Injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Clindamycin Injection
Ireland and the UK agreed to grant a Marketing Authorisation for Clindamycin Injection. A Marketing Authorisation was granted in the UK on 11 January 2010.

The full PAR for Clindamycin Injection follows this summary.

For more information about treatment with Clindamycin Injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2015.
# SCIENTIFIC DISCUSSION

**Clindamycin 150mg/ml Solution for Injection for Infusion**

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Scientific discussion

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Clindamycin 150mg/ml Solution for Injection or Infusion, in the treatment of bacterial infections, is approvable.

This is an application submitted under Article 10(1) of Directive 2001/83/EC (as amended) for Clindamycin 150mg/ml Solution for Injection or Infusion. It has been shown to be a generic medicinal product of the reference product Dalacin C Phosphate Sterile Solution (150mg/ml solution for injection-PL 00032/0042R) granted to Pharmacia Limited on 27 December 1990; hence the 10 year rule is fulfilled.

Clindamycin is a lincosamide antibacterial that is a chlorinated derivative of lincomycin. It is a mainly bacteriostatic drug used in the treatment of serious anaerobic infections, notably due to Bacteroides fragilis. It is also used for some Gram-positive infections due to pneumococci, staphylococci, and streptococci. However, because of its potential for causing pseudomembranous colitis, it is usually used only when alternative drugs are unsuitable.

Clindamycin has some antiprotozoal actions, and has been used, usually with other antiprotozoals, in various infections including babesiosis, malaria, and toxoplasmosis. It may also be used with primaquine in the treatment of pneumocystis pneumonia [Martindale: The Complete Drug Reference].

Clindamycin is active orally and parenterally. By the parental route, the following dosage is recommended

By deep intramuscular injection or by intravenous infusion, 0.6–2.7 g daily (in 2–4 divided doses); life-threatening infection, up to 4.8 g daily; single doses above 600 mg by intravenous infusion only; single doses by intravenous infusion not to exceed 1.2 g; CHILD over 1 month, 15–40 mg/kg daily in 3–4 divided doses; severe infections, at least 300 mg daily regardless of weight [SmPC of reference product].

II. QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a clear, colourless solution.

Each 1ml of solution contains clindamycin phosphate equivalent to 150mg clindamycin, as the active ingredient. Each 2ml ampoule contains 300mg clindamycin. Each 4ml ampoule contains 600mg clindamycin.
The product also contains disodium edetate, sodium hydroxide (for pH adjustment) and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in Type 1 flint glass ampoules containing 2ml or 4ml sterile, aqueous solution, packed in cardboard cartons, together with a leaflet, in pack sizes of 1 or 5 ampoules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE
Clindamycin phosphate
General Information
Nomenclature
Name: Clindamycin Phosphate

Structure

Molecular formula: C\textsubscript{18}H\textsubscript{34}ClN\textsubscript{2}O\textsubscript{8}PS

Molecular weight: 505.00

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

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

Manufacture
A satisfactory Ph Eur Certificate of Suitability (CEP) has been provided which covers the manufacture and control of the drug substance clindamycin phosphate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. The impurities for this source of drug substance fall within those listed in the Ph Eur monograph for clindamycin phosphate.

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

Batch analysis data complying with the proposed specification have been provided.

Satisfactory Certificates of Analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

The finished product manufacturer routinely tests each batch of the drug substance in accordance with the specification upon receipt.

Satisfactory Certificates of Analysis have been provided for all aspects of the container-closure system, working standards used by the active substance manufacturer, and finished product manufacturer
during validation studies. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrate the stability of the drug substance and support an appropriate retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT
Pharmaceutical Development

Drug substance
The applicant discussed the solubility of the drug substance and demonstrated that there is no solubility problem in the finished product at the used concentration of 150mg/ml.

Essential Similarity
The physico-chemical properties of the drug product have been compared with the originator product. Slight differences in the impurity profile were evident although these are not considered to be a point of issue as levels are low. Essential similarity has been adequately demonstrated.

Impurity profile
The results obtained for the reference product are consistent with the results observed for the proposed product.

Compatibility
Stability data has been submitted for the product after reconstitution with 0.9%w/v sodium chloride and 5% w/v dextrose. The data show that the product is compatible with the reconstitution diluents, 0.9%w/v sodium chloride and 5% w/v dextrose over the recommended in-use shelf-life at the recommended storage temperature and at the likely extremes of concentration.

Manufacturing Process
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation data for three pilot-scale batches has been provided with the commitment to perform validation on the first three batches of each pack size with the results being reported only if outside the proposed specification. This is satisfactory.

Control of Finished Product
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 complying with the release specification have been provided. Certificates of Analysis have been provided for any working standards used.

Stability of the Product
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years (unopened) has been set (reduced to 24 hours after opening and dilution when stored at 25°C), which is satisfactory. The precautions “Store below 25°C” and “Keep ampoules in the outer carton” are considered acceptable.

General storage conditions for the product are “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°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.”
II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic product of the originator product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator products.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website. The current labelling is presented below:
III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of clindamycin are well known.

As clindamycin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview based on literature review is thus appropriate.

The non-clinical overview has been written by a suitably qualified person. The report refers to 44 publications up to year 2008 and is satisfactory.
III.2 Pharmacology
Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
A formal Environment Assessment was not submitted. This is acceptable as no increase in environmental risk is to be expected compared to that of the reference product, since the product is a generic version of an already approved one and it is not likely to change the total market of clindamycin.

III.6 Discussion of the non-clinical aspects
In conclusion, there are no objections to the approval of Clindamycin 150mg/ml Solution for Injection or Infusion from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction.
The clinical pharmacology of clindamycin is well-known.

Clindamycin 150mg/ml Solution for Infusion or Injection is indicated for parenteral use, therefore a bioequivalence study is not required according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98).

The applicant has not conducted any clinical studies with clindamycin.

The clinical information provided in module 2 section 2.5 (Clinical overview) is all literature based. The clinical overview has been written by a suitably qualified person and is satisfactory.

IV.2 Pharmacokinetics
The clinical pharmacokinetic properties of clindamycin are well known. No new pharmacokinetic data are provided or required for this application.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of clindamycin are well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

IV.4 Clinical Efficacy
The clinical efficacy of clindamycin is well-known.

Clindamycin 150mg/ml solution for infusion or injection is indicated for parenteral use, therefore a bioequivalence study is not required according to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) and applicant has submitted

IV.5 Clinical Safety
The safety profile of clindamycin is well-known. No new safety data were submitted and none are required for an application of this type.
IV.6. Risk Management Plan
The Applicant has provided a detailed description of the pharmacovigilance system. No Risk Management Plan other than the documentation of the Pharmacovigilance system has been provided. This is acceptable for generics, since the innovator product is not subject to specific risk management procedures.

IV.7. Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Clindamycin 150mg/ml Solution for Injection or Infusion.

V. USER CONSULTATION
A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Clindamycin 150mg/ml Solution for Injection or Infusion is 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.

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

EFFICACY
No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arose from this application.

The SmPC and PIL are satisfactory and consistent with that for the 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 phosphate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Annex 1 - Table of content of the PAR update for MRP and DCP
Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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<tbody>
<tr>
<td>To update sections 4.1, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) in line with the brand leader, Dalacin C Phosphate Sterile Solution. Consequently, the Patient Information Leaflet (PIL) has been updated</td>
<td>UK/H/2220/001/IB/006</td>
<td>SmPC and PIL</td>
<td>22/04/2015</td>
<td>22/05/2015</td>
<td>Approval</td>
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</table>
Annex 1.1

Our Reference: PL 20046/0072 - 0014
Product: Clindamycin Injection 150mg/ml
Marketing Authorisation Holder: Focus Pharmaceuticals Limited
Active Ingredient(s): Clindamycin phosphate.

Type of Procedure: Decentralised
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/2220/001/IB/006

Reason:
To update sections 4.1, 4.5, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) in line with the brand leader, Dalacin C Phosphate Sterile Solution. Consequently, the Patient Information Leaflet (PIL) has been updated.

Linked / Related Variation(s) or Case(s):
Not applicable

Supporting Evidence
Revised SmPC fragments (sections), and leaflet have been provided.

Evaluation
The updated sections of the SmPC and leaflet are acceptable.

Conclusion
The updated sections of the SmPC and the leaflet are satisfactory and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision – Approved 22 May 2015.