Public Assessment Report

UKPAR

CLINDAMYCIN 150 MG CAPSULES, HARD
CLINDAMYCIN 300 MG CAPSULES, HARD

(clindamycin hydrochloride)

UK Licence No: PL 20117/0282-0283

Morningside Healthcare Limited
LAY SUMMARY
Clindamycin 150 mg Capsules, hard
Clindamycin 300 mg Capsules, hard
(clindamycin hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Clindamycin 150 mg Capsules, hard (PL 20117/0282) and Clindamycin 300 mg Capsules, hard (PL 20117/0283). It explains how the applications for Clindamycin 150 mg and 300 mg Capsules, hard, were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Clindamycin 150 mg and 300 mg Capsules, hard.

For practical information about using Clindamycin 150 mg and 300 mg Capsules, hard, patients should read the package leaflet or contact their doctor or pharmacist.

For ease of reading, these products will be referred to as Clindamycin Capsules for the remainder of this summary.

What are Clindamycin Capsules and what are they used for?
Clindamycin Capsules are a ‘generic medicine’. This means that Clindamycin Capsules are similar to ‘reference medicines’ already authorised in the European Union (EU) called Dalacin 150 mg and 300 mg capsules.

Clindamycin Capsules are used in the treatment of serious bacterial infections.

How do Clindamycin Capsules work?
These medicines contain the active ingredient clindamycin hydrochloride, which is an antibiotic. It works by stopping the bacteria which are the cause of the infection from multiplying.

How are Clindamycin Capsules used?
These medicines can only be obtained with a prescription.

In adults and elderly patients, the recommended dose of Clindamycin 150 mg Capsules is between 150 and 450 mg (1 to 3 capsules) every 6 hours, depending on the severity of the infection. The recommended dose of Clindamycin 300 mg Capsules is 300 mg (1 capsule) every 6 hours.

The recommended dose in children is between 3 and 6 mg per kg of bodyweight every six hours, depending on the severity of the infection. A doctor will work out the number of capsules that the child should have.

If a patient has to take Clindamycin Capsules for a long time, their doctor may arrange regular liver, kidney and blood tests. Patients should not miss check-ups with their doctor. Long term use can also make patients more likely to get other infections that do not respond to Clindamycin Capsules treatment.

If patients stop taking Clindamycin Capsules too soon their infection may come back again or get worse. Patients should not stop taking Clindamycin Capsules unless their doctor tells them to.

What benefits of Clindamycin Capsules have been shown in studies?
Because Clindamycin Capsules are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Dalacin 150 mg and 300 mg capsules. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Clindamycin Capsules?

2
Because Clindamycin Capsules are a generic medicine, their possible side effects are taken as being the same as those of the reference medicines, Dalacin 150 mg and 300 mg capsules.

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

For the full list of restrictions, see the package leaflet.

**Why were Clindamycin Capsules approved?**
It was concluded that, in accordance with EU requirements, Clindamycin Capsules have been shown to have comparable quality and to be bioequivalent to Dalacin 150 mg and 300 mg capsules. Therefore, the MHRA decided that, as for Dalacin 150 mg and 300 mg capsules, the benefits outweigh the identified risks and recommended that Clindamycin Capsules can be approved for use.

**What measures are being taken to ensure the safe and effective use of Clindamycin Capsules?**
A risk management plan (RMP) has been developed to ensure that Clindamycin Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Clindamycin Capsules 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 and reviewed continuously.

**Other information about Clindamycin Capsules**
Marketing Authorisations were granted in the UK on 03 November 2017.

The full PAR for Clindamycin Capsules follows this summary. For more information about treatment with Clindamycin Capsules read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2017.
SCIENTIFIC DISCUSSION

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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited Marketing Authorisations for the medicinal products Clindamycin 150 mg and 300 mg Capsules, hard (PL 20117/0282-83) on 03 November 2017.

These products are prescription-only medicines (legal classification POM).

These were applications made according to Article 10(1) of Directive 2001/83/EC, as amended. The reference product for the 150 mg strength is Dalacin C 150 mg capsules (PL 00057/0957), which was granted a Marketing Authorisation to Pfizer Limited, in the UK, on 09 August 2013. This followed a Change of Ownership from PL 00032/5007R (Pharmacia Limited), which was granted a Marketing Authorisation on 20 February 1989. Since there is no suitable reference product for the 300 mg strength authorised in the UK, reference has been made to a European reference product Dalacin C 300 mg Kapseln, which was granted a Marketing Authorisation to Pfizer Corporation Austria GmbH on 24 April 1990. It was confirmed by the Austrian competent authority that this product fulfils the legal requirements for the reference medicinal product.

Clindamycin Capsules are indicated for the treatment of serious infections caused by susceptible Gram-positive organisms, staphylococci (both penicillinase- and non-penicillinase-producing), streptococci (except Streptococcus faecalis) and pneumococci. It is also indicated in serious infections caused by susceptible anaerobic pathogens.

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

These products contain the active substance clindamycin hydrochloride, which is a lincosamide antibiotic with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Most Gram-negative aerobic bacteria, including the Enterobacteriaceae, are resistant to clindamycin. 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.

With the exception of the bioequivalence studies, no new clinical or non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Two bioequivalence studies were performed which compared the pharmacokinetics of the test products Clindamycin 150 mg and 300 mg Capsules, hard, to those of the reference products Dalacin C 150 mg capsules and 300 mg Capsules (Pfizer Corporation Austria GmbH).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application and these are satisfactory.

During assessment of these applications, advice was sought from the Expert Advisory Groups regarding clinical equivalency. The applications were presented to the Expert Advisory Groups, including the Commission on Human Medicines (CHM). The advisory groups considered the evidence and advised the MHRA. Upon provision of satisfactory responses to the outstanding points, the applications were considered to have satisfied the necessary requirements and therefore could be approved.
II QUALITY ASPECTS

II.1 Introduction
Clindamycin 150 mg Capsules, hard, are Size ‘1’ hard gelatin white capsules with ‘I 62’ marked on the cap. Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin.

Clindamycin 300mg Capsules, hard, are Size ‘0’ hard gelatin purple capsules with ‘I 63’ marked on the cap. Each capsule contains clindamycin hydrochloride equivalent to 300 mg clindamycin.

Other ingredients consist of the pharmaceutical excipients, as follows:
Lactose monohydrate, maize starch, talc, magnesium stearate.
The 150 mg capsule shells contain: gelatin and titanium dioxide (E171).
The 300 mg capsule shells contain: gelatin, erythrosine (E127), indigotine (E132) and titanium dioxide (E171).
The printing ink contains: shellac, black iron oxide (E172) and propylene glycol (E1520).

The finished product is packaged in a blister pack composed of clear, transparent 250 micron polyvinyl chloride foil and 25 micron aluminium lidding foil, in pack sizes of 7, 10, 14, 15, 20, 24, 28, 30, 56, 60, 84, 90, 100, 112 and 120 capsules. Not all pack sizes may be marketed.

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

II.2 Drug substance
rINN: Clindamycin
Chemical name: Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propylpyrrolidin-2yl]carbonyl]amino]-1-thio-L-threo-α-Dgalacto-octopyranoside hydrochloride

Structure:

![Structure Image]

Molecular formula: C_{18}H_{33}ClN_{2}O_{5}S x HCl
Molecular weight: 461.5
Appearance: White or almost white, crystalline powder
Solubility: Very soluble in water, slightly soluble in ethanol (96%)

All aspects of the manufacture and control of the active substance clindamycin hydrochloride are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability (CEP).

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate globally acceptable and stable products that could be considered generic medicinal products of the currently licensed products, Dalacin C 150 mg and 300 mg capsules (Pfizer Ltd).
A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution profiles have been provided for the applicant’s products versus the reference products.

With the exception of the capsule shells, which are controlled to an in-house specification, all excipients comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate and gelatin, none of the excipients are sourced from animal or human origin. The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. The suppliers of the gelatin have provided Certificates of Suitability from EDQM to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of BSE/TSE. The magnesium stearate is of vegetable origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on three commercial scale batches of each strength of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 2 years, with the special storage conditions of “Do not store above 30°C”.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for Clindamycin 150 mg and 300 mg Capsules, hard.

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

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The approved labelling is shown below:
Clindamycin Capsules

Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin.
Contains lactose.
Read the package leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 30°C.

Morningside Healthcare Ltd.,
115 Narborough Road, Leicester,
LE3 0PA, UK

PL 20117/0282
Clindamycin Capsules

150mg Capsules, hard
Clindamycin hydrochloride

Each capsule contains clindamycin hydrochloride equivalent to 150 mg clindamycin.
Contains lactose.

Read the package leaflet for further information.
For oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 30°C.

Morningside Healthcare Ltd.
115 Narborough Road,
Leicester, LE3 0FA, UK

PL 20117/0282
III  NON-CLINICAL ASPECTS

III.1  Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of clindamycin hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2  Pharmacology
No new pharmacology data are required for this application and none have been submitted.

III.3  Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4  Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5  Ecotoxicity/Environmental risk Assessment (ERA)
As this product is intended for generic substitution of a product that is already marketed, no increase in environmental exposure to clindamycin hydrochloride is anticipated. Thus the absence of an ERA is accepted.

III.6  Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Clindamycin 150 mg and 300 mg Capsules, hard.

IV.   CLINICAL ASPECTS

IV.1  Introduction
With the exception of the bioequivalence studies detailed below, no new clinical studies have been performed and none are required for this type of application. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2  Pharmacokinetics
In support of these applications, the applicant submitted the following bioequivalence studies:

Study 1:
An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the pharmacokinetics of the test product, Clindamycin 150 mg Capsules, hard, to those of the reference product, Dalacin C 150 mg capsules (Pfizer Corporation Austria Gmbh), in healthy, adult, human subjects, under fasting conditions.

Volunteers were given each treatment after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 16 hours post dose. Each treatment was separated by a washout period of 7 days.

A summary of the main pharmacokinetic results is presented in the table below:
The 90 % confidence intervals for clindamycin for the ratio of test/reference are within 80.00-125.00% for Cmax and AUC. Clindamycin 150 mg Capsules, hard are, therefore, considered bioequivalent to Dalacin C 150 mg capsules (Pfizer Limited).

Study 2:
An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the pharmacokinetics of the test product, Clindamycin 300 mg Capsules, hard, to those of the reference product, Dalacin C 300 mg capsules (Pfizer Corporation Austria Gmbh), in healthy, adult, human subjects, under fasting conditions.

Volunteers were given each treatment after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 16 hours post dose. Each treatment was separated by a washout period of 7 days.

A summary of the main pharmacokinetic results is presented in the table below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>3052.8773</td>
<td>2970.6099</td>
</tr>
<tr>
<td>AUC_{0-4} (ng.hr/mL)</td>
<td>11182.1913</td>
<td>11246.2551</td>
</tr>
</tbody>
</table>

The 90 % confidence intervals for clindamycin for the ratio of test/reference are within 80.00-125.00% for Cmax and AUC. Clindamycin 150 mg Capsules, hard are, therefore, considered bioequivalent to Dalacin C 150 mg capsules (Pfizer Corporation Austria Gmbh).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety
No new data on safety have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected
of occurring either in the Community or in a third country.

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Clindamycin 150 mg and 300 mg Capsules, hard.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine Risk Minimisation Measures</th>
<th>Additional Risk Minimisation Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>The risk of hypersensitivity associated with (i) use of the drug product and (ii) use of drug product in atopic individuals is described in the SPC Sections 4.3, 4.4, 4.8 and PIL Section 2.4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>The risk of pseudomembranous colitis (i) associated with use of the drug product and (ii) in patients with a history of gastrointestinal disease, especially colitis is described in the SPC Sections 4.4, 4.8 and PIL Section 2 and 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Increased coagulation tests (PT/INR) and/or bleeding on concomitant use with vitamin K antagonists</td>
<td>The risk of increased coagulation tests (PT/INR) and/or bleeding associated with concomitant use of the drug product with vitamin K antagonists is described in the SPC Section 4.5 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>Description</td>
<td>None</td>
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<tr>
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<tr>
<td>Serious cutaneous adverse reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and AGEP</td>
<td>The risk of serious cutaneous adverse reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and AGEP associated with use of the drug product is described in the SPC Section 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td></td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>The risk of hepatic dysfunction associated with (i) use of the drug product (ii) use in patients with hepatic impairment is described in the SPC Sections</td>
<td>None</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine Risk Minimisation Measures</td>
<td>Additional Risk Minimisation Measures</td>
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<tr>
<td>Increased effect of neuromuscular blocking agents on concomitant use</td>
<td>The risk of increased effect of neuromuscular blocking agents associated with concomitant use of the drug product is described in the SPC Section 4.5 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Serious haematological effects including thrombocytopenia, agranulocytosis and neutropenia</td>
<td>The risk of serious haematological effects including thrombocytopenia, agranulocytosis and neutropenia associated with the use of drug product is described in the SPC Section 4.8 and PIL Section 4 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Use during lactation</td>
<td>The risk associated with use of the drug product during lactation is described in the SPC Section 4.6 and PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.</td>
<td>None</td>
</tr>
<tr>
<td>Use in first-trimester of pregnancy</td>
<td>The SPC Section 4.6 and PIL Section 2 clearly states that clindamycin use during first-trimester of pregnancy should be used only if clearly needed as there are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.</td>
<td>None</td>
</tr>
</tbody>
</table>

**Missing Information**
IV.7 Discussion of the clinical aspects
It is recommended that Marketing Authorisations are granted for Clindamycin 150 mg and 300 mg Capsules, hard.

V. USER CONSULTATION
The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. 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 patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with clindamycin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment 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

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<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>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Y/N (version)</td>
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