IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Clindamycin 300 mg Capsules
Clindamycin hydrochloride
PA25213/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Type of marketing authorisation, main features of disease/condition etc, discussion in CMD
This mutual recognition application concerns a generic version of clindamycin and is submitted under the provisions for abridged applications under Art.10 (1) of Directive 2001/83/EC as amended, and is hence a "generic" application.
With Ireland as the Reference Member State, the applicant Chanelle Medical, Ireland is applying for the Marketing Authorisation for Clindamycin 300mg Hard Capsules in Luxembourg, Belgium and The Netherlands. The reference product is Dalacin 300mg capsule (Pfizer Oy, Finland). Dalacin has been marketed in Europe since 1975. Essential similarity is being claimed based on the results of a bioequivalence study conducted with the test product and the Finnish reference product (study ref. no. CHA-C0408/604). The study concluded that both products were bioequivalent. This study was submitted to support the Clindamycin 300 mg Hard Capsules national application. A marketing authorisation was granted in Ireland for Clindamycin 300mg hard capsules in May 2009.

Pharmacological class and mode of action
Clindamycin is included in the following Pharmacotherapeutic groups;
Anti infectives for treatment of acne, Gynaecological anti-infective – antibiotics, Antibacterials for systemic use – Lincosamides, the ATC codes are D10A F01, G01A A10 and J01FF01.
Clindamycin is a semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(S)- hydroxyl group of parent lincomycin. The mechanism of action is based on the inhibition of the protein synthesis of the bacteria. The action of clindamycin is bacteriostatic.
The submitted documentation in relation to the proposed product is of sufficient high quality in view of the present European regulatory requirements. A clinical overview, which represents an adequate summary of the dossier, has been submitted.

Indications
The indications for Clindamycin 300 mg Hard Capsules are:
Clindamycin is indicated in the treatment of severe infections due to susceptible anaerobic bacteria or gram-positive aerobic bacteria especially streptococci, staphylococci and pneumococci.

II. QUALITY ASPECTS

II.1 INTRODUCTION
This product is a hard gelatin capsule containing 300mg clindamycin, as clindamycin hydrochloride.

Composition
Each capsule contains clindamycin 300mg as an active substance and the following excipients: lactose monohydrate, maize starch, magnesium stearate, purified talc. The capsule shell contains: gelatin, patent blue V (E 131), titanium dioxide (E171) and water. All excipients comply with pharmacopoieal requirements or are adequately controlled by the manufacturer's specifications.
The EU guidelines on the use of gelatin derived from animal origin have been complied with.

Container
The capsules are packed in blister packs made from PVC/polyethylene/PVdC sealed with an aluminium lid.

II.2 2.2 DRUG SUBSTANCE
The drug substance is clindamycin hydrochloride, an established active substance described in the European Pharmacopoiea. This active substance is manufactured in line with Good Manufacturing Practise (GMP).
The drug substance specifications are considered satisfactory to control the substance quality and meets current pharmacopoieal requirements. Proposed re-test dates have been found to be acceptable. Batch analytical data demonstrating compliance with these requirements have been provided.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The hard gelatine capsule is an established pharmaceutical form and its development is adequately described in accordance with EU guidelines.

The applicant has shown that the product is stable and is essentially similar to the innovator product, Dalacin 300mg marketed in Scandanavia.

Manufacture
This product is manufactured with a conventional method, that of filling a dry powder blend into the pre-formed gelatine capsule. It is manufactured in accordance with the principles of GMP and the process has been validated in line with relevant EU/ICH guidelines.

Product Specifications
The specifications are based on those of the Ph. Eur. monograph for hard capsules with an additional test.
Batch analytical data provided shows compliance with this specification and thus the ability of the manufacturer to produce finished product of a consistent quality.

Product Stability
Stability data for the product in the proposed packaging have been provided in accordance with EU guidelines and support a shelf-life of four years with no special precautions for storage.

II.4 Discussion on chemical, pharmaceutical and bioloical aspects

Conclusion on Quality
Based on the conclusions of section II3, the quality of this product has been satisfactorily shown.

III. NON-CLINICAL ASPECTS

N/A

IV. CLINICAL ASPECTS

IV.1 INTRODUCTION
Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action against gram-positive aerobes and a wide range of anaerobic bacteria. The antibiotic activity of clindamycin is based on the inhibition of bacterial synthesis. Reversible coupling to the 50S subunit of the bacterial ribosome inhibits inter alia the translation or tRNA-bound amino acids, thereby preventing elongation of the peptide chain. Because of this, the mode of action of clindamycin is predominantly bacteriostatic. However, bactericidal activity can be achieved against some pathogens such as *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus* with therapeutic concentrations. This can be explained by the active accumulation of clindamycin in various human cells. Granulocytes, in whose lysosomes clindamycin has accumulated, reach sites of infection by chemotaxis. Very high clindamycin concentrations, which may be significantly higher than serum concentrations, have been measured in both sterile and infected abscesses. This explains both the bactericidal properties and antibacterial effects of clindamycin at sub inhibitory concentrations. At sub inhibitory concentrations, clindamycin inhibits the power of various pathogens to adhere to the surface of human cells, thereby also maintaining the immune system's power to resist infection.

IV.2 Pharmacokinetics

Pharmacokinetics
A single bioequivalence study was submitted conducted in the fasting state in healthy volunteers. This was a repeat study which was carried out because an IMB inspection of the CRC (for another product) that carried out the original bioequivalence study raised serious concerns.

Methods
Study design
A comparative randomized, single dose, two-way crossover open label study to determine the bioequivalence of Clindamycin 300 mg capsule (300 mg Clindamycin per capsule, as Clindamycin Hydrochloride) Chanelle Medical, Ireland and Dalacin® 300 Mg Capsule (300 Mg Clindamycin per capsule, as ClindamycinHydrochloride) Pfizer Oy, Finland.

Population(s) studied
28 healthy male Jordanian volunteers aged between 18 and 30 years were enrolled in the study.

Test and reference products

The test product was Clindamycin 300mg (300 mg Clindamycin per capsule, as Clindamycin Hydrochloride) Chanelle Medical, Ireland and the reference product was Dalacin® 300 mg Capsule (300 Mg Clindamycin per capsule, as Clindamycin Hydrochloride) Pfizer Oy, Finland.

Study site

The study was conducted by the International Pharmaceutical Research Center (IPRC), Sport City Circle, Amman, Jordan.
Principal investigator: Dr Usama Harb
Date of institutional review board approval of the protocol: 03/06/2008
Start date: 21/08/2008
End date 28/08/08

Study procedure

After a 10 hour overnight fast, all 28 volunteers received an oral single dose of either the test or the reference product with 240 ml water. Food and fluid intake was identical in both study periods and meals were standardised in composition and amount in both periods and were provided to subjects at set times. There was a washout period of 7 days between ingestion of test and reference products. The study was conducted between 21/08/08 and 29/08/08.

Blood sampling time points in each study period were as follows

The following blood samples for the analysis were collected immediately before (2 x 8 ml) at 0.00 (pre- dose) and at: 025, 0.50, 0,75, 100, 1 50,2 00, 3 00,4 00,6 00, 8 00, 10 00, 12 00, 14 00, 16 00 and 24 00 hours after administration of study drugs.

Analytical methods

A chromatographic HPLC-UV assay was developed at the lPRC for the determination of Clindamycin in human plasma. Samples from all subjects who completed both periods of the study were analysed. The bio-analytical method was validated according to international guidelines.

Pharmacokinetic Variables

The primary pharmacokinetic variables were Cmax, AUC_{0-t}, $AUC_{0-\infty}$. The acceptance boundaries for bioequivalence were set for clindamycin at 80-125% for the ratio of test to reference for the following variables Cmax, AUC_{0-t}, and $AUC_{0-\infty}$.
Secondary pharmacokinetic variables included t_{max}, K_e, and $T_{1/2}$

The pharmacokinetic parameters of clindamycin was estimated using standard non-compartmental methods.

Statistical methods

Statistical analysis was performed by using the Kinetica rM 2000 program, with the aid of Microsoft Excel (2002)
An analysis of variance (ANOVA) tested for sequence, period, subject (sequence) and treatment effects was used. ANOVA was performed on AUC_{0-t}, $AUC_{0-\infty}$, Cmax, t_{max}, $t_{1/2}$, K_e, Ln AUC_{0-t}, Ln $AUC_{0-\infty}$and Ln Cmax. The bioequivalence assessment is based on the statistical evaluation of AUC_{0-t} and Cmax as primary parameters.

Results

27 subjects were included in the PK analysis (one withdrew prior to commencing the second stage of the study). Two subjects had non-zero pre-dose concentrations one in each study period. Neither subject had a level of or in excess of 5% of Cmax. For the ratio of test to reference of AUC_{0-t} the point estimate was 97.17 with a 90% confidence interval (91.19, 103.54). For Cmax the point estimate was 98.63 with 90% confidence intervals of (92.51, 105.16). The 90% confidence intervals for AUC_{0-t} and Cmax lie between 80 and 125 and are therefore in line with conventional acceptance criteria for bioequivalence.
Analysis of variance of log transformed data for Cmax, AUC_{0-t} demonstrated that sequence effect, product effect and period effect did not significantly affect the outcome of the study.

Pharmacokinetic Conclusions

Given that the 90% confidence intervals for AUC_{0-t} and Cmax lie between 80 and 125 it was concluded that the proposed formulation of clindamycin hydrochloride 300mg capsule was bioequivalent to the reference product Dalacin 300mg Hard Capsule.

Safety

In the course of the bioequivalence study two subjects experienced headache. One subject experienced headache following both products and one subject following Dalacin 300mg only. All events were categorised as mild and did not require any intervention.

Assessors' overall conclusions on bioequivalence

The bioequivalence study was carried out in compliance with good clinical practice. The study design was appropriate. An appropriate reference product was used. Test conditions were standardised. Sampling intervals were appropriate as was the washout period which was in excess of the 5 elimination half-lives recommended in
Guideline on the investigation of bioequivalence
. Appropriate pharmacokinetic parameters were chosen and the correct methods used to determine them.
The 90% confidence intervals for the ratio of test to reference products lie between 80 and 125 therefore bioequivalence between Clindamycin 300mg Hard Capsule (Chanelle Healthcare) and Dalacin 300mg Hard Capsule (Pfizer) can be assumed.

IV.3 Pharmacodynamics

The pharmacodynamics of clindamycin hydrochloride is well characterised and no new pharmacodynamic studies have been undertaken. A comprehensive clinical overview has been submitted by Dr JH Meyer to support the application.

IV.4 Clinical Efficacy

Clindamycin's clinical efficacy is established for the indications sought through large numbers of clinical studies and extensive global clinical experience. The Applicant has supplied a critical review and comprehensive list of literature references that supports this marketing authorization application. The overview of clinical efficacy is adequate.

IV.5 Clinical Safety

Clindamycin has been widely available in Europe since the mid 1970s.
The most frequent side effects associated with clindamycin are gastrointestinal disorders. Both oral and parenteral administration can cause nausea, vomiting, loss of appetite and flatulence. Loose stools and diarrhoea occur frequently with incidences of up to 20% having been reported. Approximately 8-10% of patients given clindamycin develop severe pseudomembranous colitis, caused by a toxin secreted by clindamycin-resistant *C. difficile*). This adverse effect is not dose related and may occur with parenteral or oral therapy. It occurs more frequently in the elderly and in debilitated patients. If clindamycin is not stopped and the colitis not treated with an appropriate antibiotic, e.g. vancomycin, it may be fatal.
Intravenous administration of Clindamycin is reported to produce diarrhoea in up to 20% of patients after systemic administration.
The optimal dose ranges and dose regimens for clindamycin have been well established. Known and potential interactions are well documented and are included in the proposed prescribing information.The wording in the safety sections of the SmPC is in keeping with the published literature on the safety of clindamycin.
In conclusion, there is a large amount of accumulated experience with the use of clindamycin since it was first introduced into clinical practice. Its safety profile is well established and no new or different safety issues have been identified in the course of this review.

IV.6 Discussion on the clinical aspects

This mutual recognition application concerns a generic version of clindamycin and was submitted under the provisions for abridged applications under Art.10 (1) of Directive 2001/83/EC as amended, and is hence a "generic" application.
The current definition for generic medicinal products is found in Directive 2001/83/EC, Article 10(2)(b), which states that a generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. It is assumed that a generic product that meets this definition will have similar efficacy and safety profiles to that of the reference product hence there is no need to conduct specific safety and efficacy studies.
Bioequivalence has been demonstrated between Clindamycin 300 mg per capsule, as Clindamycin Hydrochloride, Chanelle Medical, Ireland and the reference product Dalacin® 300 Mg Capsule (300 Mg Clindamycin per capsule, as ClindamycinHydrochloride) Pfizer Oy, Finland. The study was conducted in Jordan under GCP conditions.

IV.7 SUMMARY OF SCIENTIFIC DISCUSSION DURING THE PROCEDURE

Day 50 comments were received from Belgium and the Netherlands. No comments were received from Luxembourg. Both Belgium and the Netherlands were of the opinion that there were potential serious risks to public health and were therefore not prepared to grant a marketing authorisation. These related to the SPC and PL. BE was of the opinion that the SPC was unacceptable because it was not in line with the recently updated SPC for Dalacin C in Belgium. NL proposed the SPC be aligned with another EU-SPC such as the SPC of DK/H/1698/001. The issues raised regarding the SPC pertained mainly to indications (4.1), dosage (4.2), presentation of adverse events (4.8) and pharmacodynamic properties (5.1).
Most of the comments were accepted by the applicant. A new version of the SPC incorporating many of the features of the Belgian and Netherlands SPC was circulated with the applicant's response at Day 60 (for further detail please see Day 68 assessment report –Annex 2). This SPC included the indications current in Belgium on the Dalacin C SPC, including the treatment of AIDS associated opportunistic infections and malaria. These indications were not acceptable to IE or NL(Day 75

comments). The applicant was asked to provide scientific justification for their inclusion. The applicant chose to remove these indications (see applicants Responses to D75 Comments). In addition to this NL suggested adopting wording from the SPC

Clindamycin solution for injection, approved through **DE/H/963/001/DC** by 14 CMS's including NL, IE and BE for 4.1 and 4.3.
The SPC circulated with the applicants responses to Day 75 Comments was acceptable to BE and IE. At Day 85 the NL agreed with the SPC but had some concerns regarding wording. These were addressed appropriately by the applicant.
It became apparent during the procedure that there was potential for inconsistency in clindamycin SPCs across and within states. The RMS recommended that Clindamycin be proposed for a harmonisation procedure through an Article 30 referral to CMDh. This was supported by the CMS and the applicant has given an undertaking to submit appropriate variations in response to the outcome of the proposed referral procedure.

V. OVERALL CONCLUSIONS

Clindamycin has been in widespread use in Europe since the mid 1970s. Its efficacy has been well established, safety issues are well understood and no new safety concerns have come to light in recent years.
A bioequivalence study undertaken in line with CHMP guidance
Guideline on the investigation of bioequivalence has demonstrated the bioequivalence of Clindamycin 300 mg (Chanelle Healthcare Ltd Ireland with Dalacin 300 mg (Pfizer, Finland).
Given that there is bioequivalence it is therefore expected that the efficacy and safety profiles of the proposed formulation will be similar to those of Dalacin 300mg capsules. Used for the proper indications the benefit risk profile of Clindamycin 300 mg (Chanelle Healthcare ltd) is likely to be similar to those of Dalacin 300 mg (Pfizer Finland).
Issues regarding the contents of the SPC have been addressed and a finalised SPC (Annex C) and PIL (Annex D) has been agreed. The concerned member states and reference member state have agreed to refer Clindamycin for an Article 30 procedure in order to ensure harmonisation of product information.
Used for the proper indications the benefit risk profile of Clindamycin 300 mg (Chanelle Healthcare Ltd) is likely to be similar to those of Dalacin 300 mg (Pfizer Finland).
Based on the review of the data on quality, safety and efficacy, and the modifications that have been undertaken to the SPC and PIL during the procedure the RMS considers that the application for Clindamycin 300mg Capsule, for the indications described in 4.1 of the SPC can be approved.
The procedure ended on 9th December and the final SPC was circulated by the HPRA.

VI. REVISION DATE

September 2023

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MA Transfer	CRN00DR0Z	SmPC section 7, 8, 10 Package Leaflet New MA Holder: EG (Eurogenerics) New PA number: PA25213/001/001	N/A	08/09/2023