CBG MEB

Public Assessment Report

Scientific discussion

Clindamycine DOUBLE-E PHARMA 300 mg capsules

(clindamycin hydrochloride)

NL License RVG: 115115

Date: 30 May 2017

This module reflects the scientific discussion for the approval of Clindamycine DOUBLE-E PHARMA 300 mg capsules. The marketing authorisation was granted on 26 March 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Clindamycine DOUBLE-E PHARMA 300 mg capsules from DOUBLE-E PHARMA Ltd.

The product is indicated in the treatment of the following infections caused by clindamycin-susceptible microorganisms. In aerobic infections, clindamycin is an alternative treatment option when other antibacterial agents are not effective or are contraindicated (e.g. in case of allergic reactions to penicillin). In anaerobic infections, clindamycin may be considered as the substance of first choice.

- Pneumonia
- Chronic sinusitis caused by anaerobic bacteria.
- Tonsillitis.
- Skin and soft tissue infections.
- Bone and joint infections, such as osteomyelitis and septic arthritis.
- Pelvic and genital infections in women, such as endometritis, pelvic cellulitis, perivaginal infections, tubo-ovarian abscesses and salpingitis, in combination with an antibiotic with proven efficacy against aerobic Gram-negative bacteria.
- Intra-abdominal infections, including peritonitis and abdominal abscesses, in combination with an antibiotic that is effective against aerobic Gram-negative bacteria.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product Dalacin 300 mg hard capsules which has been registered in Sweden by Pfizer AB since 27 March 1987. The Dutch reference product is Dalacin C 300 mg, capsules by Pfizer B.V. (NL license number 14457).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Clindamycine DOUBLE-E PHARMA is a white hard opaque capsule printed with CLIN 300. Each capsule contains 325.76 mg clindamycin hydrochloride, equivalent to 300 mg clindamycin.

The capsules are packed in PVC/Al blisters.

The excipients are:
Capsule fill – maize starch, lactose monohydrate, talc (E553b) and magnesium stearate
Capsule shell – Gelatin (E441) and titanium dioxide (E171)
Printing ink – Shellac (E904), black iron oxide (E172) and propylene glycol (E1520)

II.2 Drug Substance

The active substance is clindamycin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Clindamycin hydrochloride is white or almost white, crystalline powder and very soluble in water and slightly soluble in ethanol (96%).

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the Ph.Eur. and the additional specifications of the CEP, with an additional limit for particle size. Batch analytical data demonstrating compliance with this specification have been provided for 3 production scaled batches.

Stability of drug substance
The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The composition of the capsules was mainly determined by the composition of the innovator product and on the earlier development of a 150 mg capsule (strength not registered in the Netherlands), containing the same excipients.
Comparative dissolution studies between the batches used in the bioequivalence study were performed in media with pH 1.2, phosphate buffer pH 4.5, and phosphate buffer 6.8 (basket, 900 ml, 100 rpm). In all three media both for the test and reference product more than 85% was dissolved in 15 minutes. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and consists of dry mixing, filling and packaging. Process validation data on the product have been presented on two batches of the smallest commercial scale and on four batches of the largest commercial scale in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. for the capsule shells in-house specifications are included. The quantitative composition of the printing ink is included. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, uniformity of dosage units (by mass), dissolution, disintegration, water, assay, related substances, and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for 2 commercial scale batches stored at long-term conditions (25°C/60%RH) for up to 36 months, intermediate conditions (30°C/65%RH) for up to 12 months, and at accelerated conditions (40°C/75%RH) for up to 6 months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. When stored under accelerated conditions a change in appearance and mass was observed, therefore intermediate studies were performed. Furthermore, in one batch stored under accelerated conditions the assay decreases significantly. When stored under long term and intermediate conditions all parameters remain relatively stable. A photostability study was performed on one batch that shows that the drug product is not sensitive to light.
On the basis of the available stability data a shelf-life of 36 months with storage condition ‘Store below 30ºC’ and ‘Store in the original package to protect from moisture’ can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products. Only gelatine from suppliers that have EDQM Certificates of Suitability with resect to TSE safety are used. Therefore, a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Clindamycine DOUBLE-E PHARMA has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Clindamycine DOUBLE-E PHARMA is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Dalacin which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clindamycin hydrochloride is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Clindamycine DOUBLE-E PHARMA 300 mg capsules (DOUBLE-E PHARMA Ltd., Ireland) is compared with the pharmacokinetic profile of the reference product Dalacin 300 mg hard capsules (Pfizer AB, Sweden).

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (9 males/15 females subjects, aged 20-62 years. Each subject received a single dose (300 mg) of one of the 2 clindamycin hydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 14 hours after administration of the products.

The design of the study is acceptable. The wash-out period is adequate. A single dose, cross-over study under fasted conditions to assess bioequivalence is acceptable as, according to the SmPC, the capsules should be taken with water.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All 24 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clindamycin hydrochloride under fasted conditions.

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	13121 ± 6027	13510 ± 6273	3667 ± 1070	0.67 (0.33 – 1.30)	3.0 ± 1.0
Reference	12235 ± 4850	12710 ± 4850	3499 ± 1078	0.67 (0.33 – 1.37)	3.1 ± 1.4
***Ratio (90% CI)**	1.05	--	1.05	--	--
CV (%)	0.98 – 1.12	--	0.98 – 1.13	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Clindamycine DOUBLE-E PHARMA 300 mg capsules is considered bioequivalent with Dalacin 300 mg hard capsules.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Clindamycine DOUBLE-E PHARMA.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Colitis - Pseudomembranous enterocolitis - Hepatobilliary disorders - Antibiotic resistance - Interaction with K antagonists (e.g. warfarin, acenocoumarol and phenprocumon
Important potential risks	- Achilles tendon rupture - Encephalitis - Renal tissue damage and renal failure - Rhabdomyolysis - CNS related AEs - Cardiac AEs (i.e., arrhytmia, QT prolongation, torsade de pointes) - Drug interactions (i.e., fluvoxamine, verapamil, quetiapine) - Tinnitus - Deafness
Missing information	- Exposure during pregnancy - Exposure during breastfeeding - Exposure in children

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Dalacin. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The 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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Clindamycine DOUBLE-E PHARMA 300 mg capsules has a proven chemical-pharmaceutical quality and is a generic form of Dalacin 300 mg hard capsules. Dalacin is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Clindamycine DOUBLE-E PHARMA with the reference product, and have therefore

granted a marketing authorisation. Clindamycine DOUBLE-E PHARMA was authorised in the Netherlands on 26 March 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in pack size of the finished product; Change in the number of units (e.g. tablets, ampoules, etc.) in a pack; Change outside the range of the currently approved pack sizes (2x)	IB	22-06-2016	01-08-2016	Approved	N