CBG MEB

Public Assessment Report

Scientific discussion

Lacidipine Double-e Pharma 2 mg, 4 mg and 6 mg film-coated tablets

(lacidipine)

NL/H/2992/001-003/DC

Date: 28 July 2016

This module reflects the scientific discussion for the approval of Lacidipine Double-e Pharma 2 mg, 4 mg and 6 mg film-coated tablets. The procedure was finalised on 23 April 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
BP	British Pharmacopoeia
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 Member States have granted a marketing authorisation for Lacidipine Double-e Pharma 2 mg, 4 mg and 6 mg film-coated tablets from DOUBLE-E PHARMA Ltd.

The product is indicated for the treatment of hypertension either alone or in combination with other antihypertensive agents, including ß-adrenoceptor antagonists, diuretics, and ACE-inhibitors.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lacipil, which was first registered in Portugal by Glaxo Wellcome Farmaceutica Ltda in 1992. In the Netherlands, the innovator product is registered by Boehringer Ingelheim B.V. as Motens 2 mg and 4 mg coated tablets (NL license RVG 14772-14773).

The concerned member states (CMS) involved in this procedure were Croatia, Denmark, Latvia and Lithuania.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC. As the 6 mg reference product strength has not been authorized in the Netherlands, reference is made to the Lacipil 6 mg registration in Portugal.

II. QUALITY ASPECTS

II.1 Introduction

Lacidipine Double-e Pharma 2 mg is a white, round biconvex film-coated tablet of 7 mm marked with '2' on one side.
Lacidipine Double-e Pharma 4 mg is a white, ovoidal biconvex film-coated tablet of 12.8 x 7.2 mm with break line on both sides and marked with '4' on one side. The tablet can be divided into two equal doses.
Lacidipine Double-e Pharma 6 mg is a white, ovoidal biconvex film-coated tablets of 14.1 x 7.8 mm marked with '6' on one side.

The film-coated tablets are packed in Aluminium/Aluminium blisters.

The excipients are:
Core - povidone K 30, lactose monohydrate, magnesium stearate
Film-coating - Opadry OY-S-7335: titanium dioxide, hypromellose

The different product strengths are fully dose proportional.

II.2 Drug Substance

The active substance is lacidipine, an established active substance described in the British Pharmacopoeia (BP). The active substance is a white to pale yellow crystalline powder, practically insoluble in water. No information on polymorphs of lacidipine are described in the literature.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The synthesis consists of two synthetic steps starting. The third step is a crystallisation step. The recrystallized lacidipine is then milled and packed. No class 1 organic solvents are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the BP lacidipine monograph with an additional test for a catalyst, in accordance with the ASMF. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two pilot-scale batches by the drug product manufacturer and on three pilot-scale batches by the ASMF holder.

Stability of drug substance
Stability data on the active substance have been provided for three pilot-scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). Except for a slight increase in water content at accelerated conditions, no clear trends or changes were observed for any of the tested parameters. All parameters remained within the specified limits. The proposed retest period of 36 months and storage condition 'Store in the original package in order to protect from light' are justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were performed regarding the optimization of the composition and manufacturing process, the characterisation of the EU reference products and the performance of comparative dissolution studies. As part of the manufacturing process development it was shown that during the manufacturing process the solid state of the drug substance changed from crystalline to non-crystalline (amorphous). The amorphous form remains stable during storage of the drug product. The excipients used in the formulation are well known. The choices of the packaging and manufacturing process are justified. For the 4 mg strength compliance with the Ph.Eur. test on subdivision of tablets was demonstrated.
A bioequivalence (BE) study has been performed with the 6 mg product strength versus the corresponding reference product strength. The test batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process. The biowaiver for the 2 mg and 4 mg strengths was supported by comparative dissolution studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are fluid bed granulation, mixing with excipients of the external phase (final blending), tabletting and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. The manufacturing process is a non-standard process. Process validation data on the product has been presented for at least three full-scale batches of common blend and sufficient pilot-and full-scale compression batches for each strength.

Control of excipients
The excipients comply with Ph.Eur. or in-house requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, disintegration, dissolution, assay, related substances, water content, resistance to crushing, subdivision of tablets (4 mg strength), microbial purity, identity of titanium dioxide, residual ethanol, average mass and uniformity of dosage units. The release and shelf-life limits are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on two pilot-scale batches per strength stored at 25°C/60% RH (18-24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/Al-blisters. At both storage conditions an increase of one of the impurities is seen. No clear trends or changes were seen in any other parameter. A photostability study was not performed considering that stress studies with light on the active substance showed that lacidipine is not photostable.
The proposed shelf-life of 36 months and storage condition 'Store in the original package in order to protect from light' and 'This medicinal product does not require any special temperature storage conditions' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose monohydrate, there are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product. For lactose monohydrate compliance with the regulatory requirements was confirmed.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lacidipine 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 Lacidipine 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 Lacipil, 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lacidipine 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 member states agreed 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 Lacidipine Double-e Pharma 6 mg (DOUBLE-E PHARMA Ltd, Ireland) is compared with the pharmacokinetic profile of the reference product Lacipil 6 mg film-coated tablets (GlaxoSmithKline, Italy). Two test formulations were used: Test Product A is the formulation applied for. In the Test Product B the quantity of PVP K 30 is higher and about 10% of the drug substance is added in the extra-granular phase. Only the results of Test Product A are presented below.

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.

Biowaiver
According to the CPMP guideline "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,
c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).
d) appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing.

As these conditions have been fulfilled, a biowaiver was granted for the 2 mg and 4 mg strengths.

Bioequivalence studies
Design
A single-dose, randomised, three-period, two-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 72 healthy subjects (54 males/18 females), aged 20-43 years. Each subject received a single dose (6 mg) of one of the 3 lacidipine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 3 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.167, 0.33, 0.66, 1.0, 1.3, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8, 10, 12, 16, 24, 48 and 72 hours after administration of the products.

One bioequivalence study with the highest dose under fasting conditions is acceptable for this application.

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
Sixty eight subjects completed the study for all periods and were included in the analysis. The four dropouts were due to medical reasons or positive pregnancy test.

Table-A: Descriptive Statistics of Formulation Means for Lacidipine (n= 68) (A Vs C)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product-A	Reference Product-C
T_{max} (h)*	1.333 (0.667 - 4.000)	1.333 (0.667 - 4.000)
C_{max} (ng / mL)	10.413 ± 6.0184	10.226 ± 6.3230
AUC_{0-t} (ng.h / mL)	37.825 ± 21.6807	38.531 ± 23.5745
$AUC_{0-\infty}$ (ng.h / mL)	41.848 ± 25.3172	42.081 ± 26.8996
λz (1 / h)	0.031 ± 0.0229	0.030 ± 0.0184
$t_{½}$ (h)	27.966 ± 10.7651	27.116 ± 9.4262
AUC_%Extrap_obs (%)	8.318 ± 4.0242	7.482 ± 3.5207

*T_{max} is represented in median (range) value.

Table-B: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Lacidipine (n= 68) (A Vs C)

Parameters (Units)	(ln-transformed) Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Test Product-A	Reference Product-C	Ratio (A / C)%	
C_{max} (ng / mL)	8.669	8.389	103.3	91.87-116.25
AUC_{0-t} (ng.h / mL)	31.965	32.210	99.2	91.08 - 108.12
$AUC_{0-\infty}$ (ng.h / mL)	34.902	34.843	100.2	92.06 - 108.99

Conclusion on bioequivalence study

For test formulation A the 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 80-125%. Based on the submitted bioequivalence study Lacidipine Double-e Pharma 6 mg is considered bioequivalent with Lacipil 6 mg.

Test formulation B was not demonstrated to be bioequivalent. However, this is not a concerns, as this formulation does not correspond with the final Lacidipine Double-e Pharma formulation of this application.

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 Lacidipine Double-e Pharma.

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions including skin rashes, angioedema and urticarial • Reduced coronary blood-flow in patients with aortic stenosis (myocardial ischaemia, angina pectoris, myocardial infarction) • Mood disorders (depression) • Elevated alkaline phosphatase
Important potential risks	Potential Risks • Cardiac conduction disorders • QT interval prolongationExtrapyramidal syndrome •
Missing information	• Safety in treatment of malignant hypertension. • Safety in paediatric and adolescent patients (≤ 18 yrs. of age) • Safety in pregnancy

The member states 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 Lacipil. 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 (PL) has not been evaluated via a user consultation study. The MAH submitted a bridging report referring to an approved English PL of Lacidipine 4 mg and 6 mg (Rivopharma). A comparison of content, format, layout and design of the package leaflets was made. The member states agree that bridging is justified and no additional testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lacidipine Double-e Pharma 2 mg, 4 mg and 6 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Lacipil film-coated tablets. Lacipil 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lacidipine Double-e Pharma with the reference product, and

have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 April 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name of the medicinal product in Croatia.	NL/H/2992/ 001-003/IB/ 001	IB	1-10-2015	31-10-2015	Approval	N