Public Assessment Report

Decentralised Procedure

Lacidipine 4 mg Film-coated Tablets

Lacidipine 6 mg Film-coated Tablets

(UK/H/5192/001-002/DC)

PL 33155/0021

PL 33155/0022

Rivopharm UK Ltd.
**Lay Summary**

This is a summary of the Public Assessment Report (PAR) for Lacidipine 4 mg Film-coated Tablets (PL 33155/0021) and Lacidipine 6 mg Film-coated Tablets (PL 33155/0022). These products may be referred to as Lacidipine Tablets in this report. This summary explains how Lacidipine Tablets 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 Lacidipine Tablets.

For practical information about using Lacidipine Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

**What are Lacidipine Tablets and what are they used for?**
Lacidipine Tablets are generic medicines. This means that Lacidipine Tablets contain the same active substance as, and are similar to, reference medicines already authorised in the European Union (EU) called Lacipil 4 mg and 6 mg tablets.

Lacidipine Tablets taken regularly as prescribed by a doctor help to lower blood pressure.

**How are Lacidipine Tablets used?**
The usual starting dose of Lacidipine Tablets is 2 mg every morning but after 3-4 weeks this may be increased to 4 mg every morning. If necessary, the dose may be increased again to 6 mg every morning, which is the maximum daily dose. Tablets should be swallowed whole with water and must not be taken with grapefruit juice.

**How do Lacidipine Tablets work?**
Lacidipine Tablets belong to a group of medicines called calcium channels blockers which help to relax blood vessels so that they get wider. This helps the blood to flow more easily and lowers blood pressure.

**How have Lacidipine Tablets been studied?**
Because Lacidipine Tablets are generic medicines, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicines, Lacipil 4 mg and 6 mg tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Lacidipine Tablets?**
Because Lacidipine Tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and risks are taken as being the same as the reference medicines.

**Why are Lacidipine Tablets approved?**
It was concluded that, in accordance with EU requirements, Lacidipine Tablets have been shown to have comparable quality and to be bioequivalent to Lacipil. Therefore, the view was that, as for Lacipil, the benefit outweighs the identified risk.
What measures are being taken to ensure the safe and effective use of Lacidipine Tablets?
A risk management plan has been developed to ensure that Lacidipine Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Lacidipine Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Lacidipine Tablets
The Marketing Authorisations for Lacidipine Tablets were granted on 19 November 2013.

The full PAR for Lacidipine Tablets follows this summary.

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

This summary was last updated in January 2014.
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Module 1

Information about Decentralised Procedure

<table>
<thead>
<tr>
<th>Names of the products in the Reference Member State</th>
<th>Lacidipine 4 mg Film-coated Tablets Lacidipine 6 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of application</td>
<td>Article 10 (1), generic</td>
</tr>
<tr>
<td>Name of the drug substance</td>
<td>Lacidipine</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code) of the medicinal products</td>
<td>Dihydropyridine derivatives (C08CA09)</td>
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<tr>
<td>Pharmaceutical form and strength of the medicinal product</td>
<td>Film-coated tablets; 4 mg and 6 mg</td>
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<tr>
<td>Reference numbers for the Decentralised Procedure</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<tr>
<td>Member States concerned</td>
<td>FR, IT, PL</td>
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<td>10 December 2012</td>
</tr>
<tr>
<td>End date of the Decentralised Procedure</td>
<td>8 November 2013 (day 208)</td>
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<tr>
<td>Marketing Authorisation numbers</td>
<td>PL 33155/0021 PL 33155/0022</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Rivopharm UK Ltd. 6th Floor, 28 Kingsway London WC2B 6JR United Kingdom</td>
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</table>
Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

Product Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

The following text is the approved label text for the products. No label mock-ups have been provided. In accordance with medicines legislation, the products shall not be marketed in the UK until approval of the label mock-ups has been obtained.

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<tbody>
<tr>
<td>BLISTER</td>
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</tbody>
</table>

1. NAME OF THE MEDICINAL PRODUCT

Lacidipine 4 mg Film-coated Tablets
lacidipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Rivopharm UK Ltd.

3. EXPIRY DATE

EXP: {MM/YYYY}

4. BATCH NUMBER

Lot:

5. OTHER
DCPAR; LACIDIPINE 4 MG FILM-COATED TABLETS AND LACIDIPINE 6 MG FILM-COATED TABLETS, PL 33155/0021-0022

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
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</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Lacidipine 4 mg Film-coated Tablets
lacidipine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 4 mg lacidipine

3. **LIST OF EXCIPIENTS**

Contains Lactose Monohydrate
See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

<table>
<thead>
<tr>
<th>14 film-coated tablets</th>
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</thead>
<tbody>
<tr>
<td>28 film-coated tablets</td>
</tr>
</tbody>
</table>

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use
For oral use

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from light

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**
12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription
POM

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

Lacidipine 4 mg Film-coated Tablets
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<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<td>BLISTER</td>
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<table>
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<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<td>lacidipine</td>
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<td>Rivopharm UK Ltd.</td>
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<th>4. BATCH NUMBER</th>
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</thead>
<tbody>
<tr>
<td>Lot:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lacidipine 6 mg Film-coated Tablets
lacidipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 6 mg lacidipine

3. LIST OF EXCIPIENTS

Contains Lactose Monohydrate
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
Rivopharm UK  
6th floor, 28 Kingsway  
London WC2B 6JR  
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription  
POM

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

Lacidipine 6 mg Film-coated Tablets
Module 5

Scientific Discussion during Initial Procedure

I. INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Lacidipine Tablets could be approved. These prescription only medicines (POM) are intended for the treatment of essential hypertension.

These Decentralised applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as so-called generic applications. The reference medicinal products for these applications are Lacipil 4 mg and 6 mg, which were first authorised to GlaxoSmithKline in 1998. The UK reference product is Motens 4 mg Tablets (PL 19494/0255). The reference products have been authorised in the EEA for at least 10 years, therefore, the legal basis of these applications is acceptable.

Lacidipine is a specific and potent calcium antagonist with a predominant selectivity for calcium channels in the vascular smooth muscle. Its main action is to dilate peripheral arterioles, reducing peripheral vascular resistance and lowering blood pressure.

An open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study comparing Lacidipine 6 mg Film-coated Tablets with Lacipil Film coated Tablets 6 mg was conducted in support of these applications. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on the products being generic medicinal products of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at Day 208 of the procedure on 8 November 2013. After a subsequent national phase, the Marketing Authorisations were granted in the UK on 28 November 2013.
II. ABOUT THE PRODUCT

| Name of the products in the Reference Member State | Lacidipine 4 mg Film-coated Tablets  
Lacidipine 6 mg Film-coated Tablets |
| Name of the drug substance | Lacidipine |
| Pharmacotherapeutic classification (ATC code) | Dihydropyridine derivatives (C08CA09) |
| Pharmaceutical form and strengths | Film-coated tablets; 4 mg and 6 mg |
| Reference numbers for the Decentralised Procedure | UK/H/5192/001/DC  
UK/H/5192/002/DC |
| Reference Member State | United Kingdom |
| Member States concerned | FR, IT, PL |
| Marketing Authorisation numbers | PL 33155/0021  
PL 33155/0022 |
| Name and address of the authorisation holder | Rivopharm UK Ltd.  
6th Floor, 28 Kingsway  
London WC2B 6JR  
United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE: LACIDIPINE

Chemical name: Diethyl (E)-4-{2-[(tert-butoxycarbonyl)vinyl]phenyl}-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate
CAS registry number: 103890-78-4
Molecular formula: C_{26}H_{33}NO_{6}
Relative molecular mass: 455.55
Structural formula:

![Structural formula of Lacidipine](image)

Description: A white to pale yellow crystalline powder, practically insoluble in water, freely soluble in acetone, sparingly soluble in absolute alcohol. Lacidipine has a melting point of approximately 178° C, a pH of 5.0 (in 10% suspension) and a pKa \(<2.0.

An Active Substance Master File (ASMF) has been provided by the manufacturer, covering the manufacture and control of the active substance.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
MEDICINAL PRODUCTS: LACIDIPINE 4 MG FILM-COATED TABLETS
LACIDIPINE 6 MG FILM-COATED TABLETS

Description and composition
Lacidipine 4 mg Film-coated Tablets are white, ovoidal biconvex film-coated tablets with a scoreline on both sides and embossed with ‘4’ on one side. The tablet can be divided into two equal doses. Lacidipine 6 mg Film-coated Tablets are white, ovoidal biconvex film-coated tablets, embossed with ‘6’ on one side.

Lacidipine 4 mg Film-coated Tablets and Lacidipine 6 mg Film-coated Tablets contain 4 mg and 6 mg lacidipine, respectively, and the excipients Povidone K 30, lactose monohydrate, magnesium stearate (which make up the tablet core) and the film-coating Opadry OY-S-7335, which comprises titanium dioxide and hypromellose.

Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their European Pharmacopoeia monographs with the exception of Opadry OY-S-7335, however, as Opadry OY-S-7335 is composed of European Pharmacopoeia components, this is acceptable.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

Pharmaceutical development
The aim of the pharmaceutical development was to obtain generic formulations with similar in vitro dissolution profiles and in vivo pharmacokinetic performance to the reference products.

Comparative in-vitro dissolution and impurity profiles have been provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the medicinal products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of medicinal products
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.
Container closure system
The tablets are packaged in aluminium/aluminium blisters placed into cardboard boxes containing 14 or 28 film-coated tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the relevant regulations concerning use of materials in contact with food. Not all pack sizes may be marketed.

Stability
Stability studies were performed on batches of medicinal product in the packaging proposed for marketing and in accordance with current guidelines. The stability data support a shelf-life of 24 months when the storage precaution ‘Store in the original package in order to protect from light’ is applied.

Product literature
The SmPCs, PILs and labelling are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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 the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) forms
The MAA forms are satisfactory from a pharmaceutical perspective.

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

Conclusion
The grant of Marketing Authorisations is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacological, pharmacokinetic and toxicological properties of lacidipine are well known, no further non-clinical studies are required and none have been provided.

Non-clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Environmental Risk Assessment
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all lacidipine-
containing products, which, in turn, is unlikely to increase exposure of the environment to lacidipine.

**Product Literature**
The product literature is acceptable from a non-clinical point of view.

**Conclusion**
The grant of Marketing Authorisations is recommended.

### III.3 CLINICAL ASPECTS

The clinical pharmacology of lacidipine is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic (PK) data are provided or required for these applications.

**Biowaiver**
The applicant has submitted a single bioequivalence study using the 6mg dose strength only. The requirements of the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) have been met with regards to a claim for a biowaiver for the 4mg dose strength, on the following basis:

1) The 4 mg and 6 mg strengths are manufactured by the same manufacturer and process
2) The qualitative compositions of the two strengths are the same
3) The quantitative compositions of excipients for the two strengths are proportional.
4) Linear PK has been established across this dose range for lacidipine
5) Dissolution data confirm that the dissolution profiles of the two strengths are similar.

Linearity of lacidipine PK for doses between 2 and 6 mg after single and multiple oral doses in healthy volunteers has been reported in the literature. The dissolution data and other biowaiver criteria are acceptable.

**Bioequivalence study**

**Study design**
The study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study comparing Lacidipine 6 mg Film-coated Tablets with Lacipil Film coated Tablets 6 mg.

A single tablet of each study medication was given to fasted subjects under standard conditions, with a washout of at least 8 days between study periods.

Blood samples were collected from each subject in each period at pre-dose and at intervals up to 72 hours following drug administration. The plasma samples from the subjects were analysed for lacidipine using a validated method.
In all, 67 subjects completed the clinical phase of the study successfully. Plasma samples from all the 67 subjects were considered in the PK analysis and the results are presented below:

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(In-transformed) Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product-A</td>
<td>Reference Product-C</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng / mL)</td>
<td>8.669</td>
<td>8.389</td>
</tr>
<tr>
<td>$AUC_{\text{0-4}}$ (ng.h / mL)</td>
<td>31.965</td>
<td>32.210</td>
</tr>
<tr>
<td>$AUC_{\text{0-4\infty}}$ (ng.h / mL)</td>
<td>34.902</td>
<td>34.843</td>
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</table>

The 90% confidence intervals for AUC and $C_{\text{max}}$ were within the acceptance range of 80.00 to 125.00 %. Bioequivalence between the test product and reference product has been adequately demonstrated.

**Clinical Efficacy**
No new efficacy data are presented for these applications and none are required.

**Clinical Safety**
With the exception of the data generated during the bioequivalence study, no new safety data are presented for these applications and none are required. No new or unexpected safety issues arose during the bioequivalence study.

**Pharmacovigilance System**
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

**Risk Management Plan**
The applicant has submitted a Risk Management Plan according to the format specified in GVP module V. This is acceptable.

**Clinical Overview**
A Clinical Overview written by an appropriately qualified physician has been provided and is a satisfactory summary of the clinical aspects of the dossier.

**Product Literature**
All product literature (SmPCs, PILs and labelling) is clinically acceptable. The SmPCs are consistent with those for the reference products. The PILs are consistent with the details in the SmPCs and in line with the current guidelines. The labelling is in line with the current guidelines.

**Conclusion**
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Lacidipine Tablets are 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. Bioequivalence has been demonstrated between the applicant’s 6 mg tablet and Lacipil Film coated Tablets 6 mg and, as biowaiver criteria have been met, the results of this study can be extrapolated to the 4 mg strength tablets.

With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of lacidipine is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are in line with those for the reference products and current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with lacidipine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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