Public Assessment Report

UKPAR

Lacidipine 6 mg Film-Coated Tablets

(lacidipine)

UK Licence Numbers: PL 08553/0528

Dr. Reddy’s Laboratories (UK) Ltd.
LAY SUMMARY

Lacidipine 6 mg Film-Coated Tablets
(lacipidine)

This is a summary of the Public Assessment Report (PAR) for Lacidipine 6 mg Film-Coated Tablets (PL 08553/528). It explains how Lacidipine 6 mg Film-Coated Tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Lacidipine 6 mg Film-Coated Tablets.

The product will be referred to as Lacidipine throughout the remainder of this public assessment report (PAR).

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

What is Lacidipine and what is it used for?
Lacidipine is a ‘generic medicine’. This means that Lacidipine is similar to a ‘reference medicine’ already authorised in the EU called Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy).

Lacidipine tablets, taken regularly as prescribed by the patient’s doctor, will help to lower their blood pressure (to treat hypertension).

How does Lacidipine work?
This medicine contains the active ingredient lacidipine which belongs to a group of medicines called ‘calcium channel blockers’. Lacidipine helps to relax the blood vessels so that they get wider. This helps the blood to flow more easily and lowers the blood pressure.

How is Lacidipine used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are unsure.

It is important to take the right number of tablets at the right time of day.
- The usual starting dose is 2 mg every morning.
- 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.
- Swallow the tablets whole with a drink of water.
- Do not take with grapefruit juice.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Lacidipine is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.
What benefits of Lacidipine have been shown in studies?
Because Lacidipine is a generic medicine, studies have been limited to tests to determine that it is bioequivalent to the reference medicine Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Lacidipine?
Because Lacidipine is a generic medicine and is bioequivalent to the reference medicine Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy), its benefits and possible side effects are taken as being the same as the reference medicine.

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

For the full list of all side effects reported with Lacidipine, see section 4 of the package leaflet available on the MHRA website.

Why was Lacidipine approved?
It was concluded that, in accordance with EU requirements, Lacidipine has been shown to have comparable quality and to be bioequivalent to Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy). Therefore, the MHRA decided that, as for Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy); the benefits are greater than the risks and recommended that it can be approved for use.

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

Other information about Lacidipine
A Marketing Authorisation was granted in the UK on 21 March 2018.

The full PAR for Lacidipine follows this summary.

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

This summary was last updated in April 2018.
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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 Dr. Reddy’s Laboratories (UK) Ltd a marketing authorisation for the medicinal product Lacidipine (PL 08553/0528) on 21 March 2018. The product is a prescription only medicine (POM) indicated in adults for the treatment of hypertension either alone or in combination with other antihypertensive agents, including β-adrenoceptor antagonists, diuretics, and ACE-inhibitors.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic application. The European reference medicinal product for this application is Lacirex 6 mg tablets which were originally authorised to Laboratori Guidotti SpA (MA number AIC 027831041, 027831054) on 10 November 1998 in Italy.

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.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Lacidipine outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 6 mg lacidipine as the active ingredient. Other ingredients consist of the pharmaceutical excipients:

**Tablet core**
Lactose monohydrate, povidone (K-30), crospovidone and magnesium stearate.

**Film-coating (Opadry White OY-58900)**
Hypropellose 5cP (E464), titanium dioxide (E171) and macrogol/PEG 400.

The finished product is packaged in aluminium/aluminium blister (OPA/Alu/PVC-Alu) packs containing 28 tablets.

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

**INN:** Lacidipine

**Chemical name:** Diethyl (E)-4-{2-[tert-butoxycarbonyl]vinyl}phenyl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate

**Structure:**

![Lacidipine Structure](image)

**Molecular formula:** C_{26}H_{33}NO_{6}

**Molecular weight:** 455.6

**Appearance:** A white to pale yellow crystalline powder.

**Solubility:** Practically insoluble in water; freely soluble in acetone; sparingly soluble in absolute ethanol.

Lacidipine is the subject of an active substance master file (ASMF).

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.
Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

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 supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious tablets containing 6 mg, lacidipine per tablet, that are generic versions of the reference product Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy). A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film-coating (Opadry White OY-58900) which is compliant with a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. The marketing authorisation holder has committed to conduct process validation on future commercial scale batches. The process validation protocol to be followed for full-scale production batches has also been provided and is satisfactory.

Finished Product Specifications
The finished product release and shelf life specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years for the unopened blisters with the storage conditions ‘this medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of lacidipine are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Lacidipine 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.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of lacidipine is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of lacidipine.

Based on the data provided, Lacidipine can be considered bioequivalent to Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
A balanced, randomised, two-treatment, three-period, three-sequence, partial replicate, single dose, crossover oral bioequivalence study of the applicant’s test product Lacidipine 6 mg Film-Coated Tablets (Dr. Reddy’s Laboratories (UK) Ltd) versus the reference product Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy) in healthy, adult, subjects under fasting conditions.
Subjects were administered a single oral dose (1 x 6 mg tablet) of the test or reference product under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 15 days. The pharmacokinetic results are presented below:

**Table: Summary of pharmacokinetic data for lacidipine (geometric mean ratio, and 90% Confidence Interval):**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test Product-T</th>
<th>Reference Product-R</th>
<th>Ratio (T/R) (%)</th>
<th>90% Confidence Interval</th>
<th>Intra Subject CV of Reference Product-R (%)</th>
<th>Power (%)</th>
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<tbody>
<tr>
<td>lnAUC₀₋ₚ</td>
<td>28.227</td>
<td>26.076</td>
<td>108.2</td>
<td>100.89 - 116.15</td>
<td>39.9</td>
<td>100.0</td>
</tr>
<tr>
<td>lnAUC₀₋∞</td>
<td>30.844</td>
<td>28.738</td>
<td>107.3</td>
<td>100.08 - 115.10</td>
<td>39.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

AUC₀₋ₚ  area under the plasma concentration-time curve from zero to t hours
AUC₀₋∞ area under the plasma concentration-time curve from zero to ∞ hours
C_max  maximum plasma concentration

**Study conclusion**
The 90% confidence intervals of the test/reference ratio for AUC and C_max values for lacidipine lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr*). Thus, the data support the claim that the applicant’s test product Lacidipine 6 mg Film-Coated Tablets (Dr. Reddy’s Laboratories (UK) Ltd) is bioequivalent to the reference product Lacirex 6 mg tablets (Laboratori Guidotti SpA, Italy).

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

**IV.4 Clinical efficacy**
No new efficacy data were submitted and none were required for applications of this type.

**IV.5 Clinical safety**
No new safety data were submitted and none are required.
IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form that would have any implications for safety.

In line with the reference product, the MAH proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the PIL). This is agreed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:
- At the request of the MHRA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

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 language used for the purpose of user testing the PIL was English.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product 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 product is bioequivalent to the marketed reference product and their risks and benefits are considered similar. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
PAR Lacidipine 6 mg Film-Coated Tablets

PL 08553/0528
Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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