

**Lacidipine 2 mg Film-Coated Tablets
PL 08553/0502**

**Lacidipine 4 mg Film-Coated Tablets
PL 08553/0503**

UK Public Assessment Report

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LAY SUMMARY

Lacidipine 2 mg Film-Coated Tablets
Lacidipine 4 mg Film-Coated Tablets
(lacidipine)

This is a summary of the public assessment report (PAR) for Lacidipine 2 and 4 mg Film-Coated Tablets (PL 08553/0502 - 0503). This PAR explains how Lacidipine 2 and 4 mg Film-Coated 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 2 and 4 mg Film-Coated Tablets.

For practical information about using Lacidipine 2 and 4 mg Film-Coated Tablets, patients should read the patient information leaflet (PIL) or contact their doctor or pharmacist.

What are Lacidipine 2 and 4 mg Film-Coated Tablets and what are they used for?

Lacidipine 2 and 4 mg Film-Coated Tablets are 'generic medicines'. This means that Lacidipine 2 and 4 mg Film-Coated Tablets are similar to 'reference medicines' already authorised in the European Union (EU) called Motens 2 mg and 4 mg tablets. Lacidipine 2 and 4 mg Film-Coated Tablets are used to treat high blood pressure (hypertension).

How do Lacidipine 2 and 4 mg Film-Coated Tablets work?

The active ingredient in Lacidipine 2 and 4 mg Film-Coated Tablets is lacidipine, which belongs to a group of medicines called 'calcium channel blockers'. Lacidipine acts at specific sites within the blood vessels, causing them to relax and become wider. This allows the blood to flow more easily and reduces blood pressure.

How are Lacidipine 2 and 4 mg Film-Coated Tablets used?

Lacidipine 2 and 4 mg Film-Coated Tablets are taken orally, and should be taken at the same time each day, preferably in the morning. The prescribing doctor will decide the dose. The usual starting dose is 2 mg every day. After 3 to 4 weeks, this may be increased to 4 mg every day and, if necessary, increased again to the maximum dose of 6 mg every day.

Lacidipine 2 and 4 mg Film-Coated Tablets can only be obtained with a prescription.

What benefits of Lacidipine 2 and 4 mg Film-Coated Tablets have been shown in studies?

Because Lacidipine 2 and 4 mg Film-Coated Tablets are generic medicines, studies in patients have been limited to tests to determine that the highest strength medicine, Lacidipine 4 mg Film-Coated Tablets, is bioequivalent to the reference medicine Motens 4 mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

It was deduced from these tests that Lacidipine 2 and 4 mg Film-Coated Tablets are comparable to equivalent strengths of the reference medicines Motens 2 and 4mg Tablets.

What are the possible side effects of Lacidipine 2 and 4 mg Film-Coated Tablets?

Because Lacidipine 2 and 4 mg Film-Coated Tablets are 'generic medicines' and are bioequivalent to the reference medicines, their benefits and possible side effects are taken as being the same as the reference medicines.

Why are Lacidipine 2 and 4 mg Film-Coated Tablets approved?

It was concluded that, in accordance with EU requirements, Lacidipine 2 and 4 mg Film-Coated Tablets have been shown to have comparable quality and to be bioequivalent to the reference medicines Motens 2 and 4 mg Tablets. Therefore, the Medicines and Healthcare products Regulatory Agency (MHRA) decided that, as for the reference medicines Motens 2 and 4 mg tablets, the benefits outweigh the identified risks. The MHRA therefore recommended that Lacidipine 2 and 4 mg Film-Coated Tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Lacidipine 2 and 4 mg Film-Coated Tablets?

A risk management plan has been developed to ensure that Lacidipine 2 and 4 mg Film-Coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the patient information leaflet for Lacidipine 2 and 4 mg Film-Coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Side effects reported by patients and healthcare professionals are reviewed on an ongoing basis.

Other information about Lacidipine 2 and 4 mg Film-Coated Tablets

The marketing authorisations for Lacidipine 2 and 4 mg Film-Coated Tablets were granted on 20 August 2014.

The full PAR for Lacidipine 2 and 4 mg Film-Coated Tablets follows this summary. For more information about treatment with Lacidipine 2 and 4 mg Film-Coated Tablets, read the patient information leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2014.

Lacidipine 2 mg Film-Coated Tablets
Lacidipine 4 mg Film-Coated Tablets
PL 08553/0502 - 0503

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted marketing authorisations to Dr. Reddy's Laboratories (UK) Limited for Lacidipine 2 and 4 mg Film-Coated Tablets (PL 08553/0502 - 0503) on 20 August 2014.

These products are prescription-only medicines (POM), indicated in adults for the treatment of hypertension either alone or in combination with other antihypertensive agents, including β -adrenoceptor antagonists, diuretics, and angiotensin-converting-enzyme inhibitors (ACE-inhibitors). A comprehensive description of the indications and posology is given in the summary of product characteristics (SmPC).

These marketing authorisations have been granted pursuant to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Motens 2 and 4 mg Tablets (PL 00015/0188 - 0189), which were authorised to Boehringer Ingelheim Limited on 29 April 1993. On 12 April 2013, the marketing authorisations for the reference products were updated by a change of ownership to the current marketing authorisation holder, Glaxosmithkline UK Limited (PL 19494/0254 - 0255).

These medicinal products contain the active substance lacidipine, which is a specific and potent calcium antagonist with a predominant selectivity for calcium channels in vascular smooth muscle. Its main action is to dilate peripheral arterioles, reducing peripheral vascular resistance and lowering blood pressure.

No new non-clinical data were provided with these applications, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

With the exception of bioequivalence data, no new clinical data were provided with these applications. One bioequivalence study was performed, which compared the pharmacokinetics of the applicant's Lacidipine 4 mg Film-Coated Tablets with those of Motens 4 mg tablets (Boehringer Ingelheim Limited) in healthy subjects under fasted conditions. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

A summary of the pharmacovigilance system and risk management plan have been provided with these applications and are satisfactory.

The MHRA considered that the applications could be approved and the licences were granted on 20 Aug 2014.

PHARMACEUTICAL ASSESSMENT

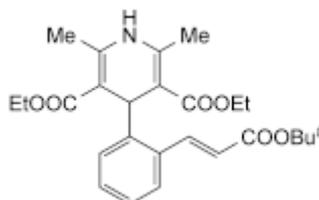
DRUG SUBSTANCE

Lacidipine

INN: Lacidipine

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

Chemical Structure:



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 and dichloromethane, sparingly soluble in ethanol.

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

Synthesis of the drug 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 pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance, which is in-line with the current BP monograph for lacidipine with additional tests undertaken by the ASMF holder. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Satisfactory 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 to contain the active substance. 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.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, povidone (K-30), crospovidone, magnesium stearate, and an Opadry White film-coating excipient (composed of hypromellose 5cP (E464), titanium dioxide (E171), Macrogol/PEG 400).

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of the film-coating excipient. This film-coating excipient complies with a suitable in-house specification. Suitable batch analysis data have been provided for all excipients, showing compliance with their respective specifications.

None of the excipients are sourced from animal or human origin, except for lactose monohydrate. A declaration has been provided for the lactose supplier stating that the lactose is produced from calf rennet alone and satisfies the requirements of the Note for Guidance (NfG) on the transmission of spongiform encephalopathy (EMA/410/01 rev.3), which is acceptable. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to formulate stable products, containing 2 and 4 mg of the active ingredient lacidipine, which could be considered bioequivalent to the reference products Motens 2 and 4 mg Tablets (Boehringer Ingelheim Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the products used in the bioequivalence study: the applicant's test product, Lacidipine 4 mg Film-Coated Tablets, versus versus the reference product, Motens 4 mg Tablets.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of both strengths of product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System

Both strengths of tablets are packaged in oriented polyamide/aluminium/polyvinylchloride-aluminium blisters, in pack sizes of 28 tablets, which are further packed into a carton.

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.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of both strengths of finished product, packed in the packaging proposed for marketing. The data from

these studies support a shelf-life of 2 years, with special storage conditions of “Store in the original package in order to protect from light”.

Suitable post approval stability commitments have been provided.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPCs, PIL and labels are pharmaceutically acceptable.

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, as amended. The results indicate that the patient information 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 pharmaceutically satisfactory.

Quality Overall Summary (Expert report)

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of marketing authorisations is recommended.

NON-CLINICAL ASSESSMENT

These applications are for generic medicinal products of Motens 2 and 4 mg Tablets (PL 19494/0254 – 0255; Glaxosmithkline UK Limited), which have been licensed within the EEA for over 10 years.

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

No environmental risk assessment has been provided with this application. As this product is intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, balanced, randomised, two-treatment, three sequence, three-period, partial replicate, single-dose, oral bioequivalence study to compare the pharmacokinetics of the test product Lacidipine 4 mg Film-Coated Tablets versus the reference product Motens 4 mg Tablets (Boehringer Ingelheim Limited) in healthy subjects under fasting conditions.

Volunteers received the test or reference treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 48 hours post dose. The two treatment periods were separated by a minimum 1 week washout period.

The main pharmacokinetic results for the lacidipine are presented below:

Parameters	Geometric Least Square Means			90% Confidence Interval	Intra Subject CV (%)
	Reference product (R)	Test product (T)	T/R Ratio (%)		
C_{max}	4.938	4.643	94.0	86.27 - 102.47	40.5
AUC_{0-t}	15.799	17.497	110.7	103.33 - 118.70	32.2
AUC_{0-INF}	17.346	19.163	110.5	103.20 - 118.27	31.6

The confidence intervals were within the acceptance criteria of 80 - 125 %. Based on these results, the proposed product, Lacidipine 4 mg Film-Coated Tablets, can be considered to be bioequivalent with the reference product Motens 4 mg Tablets.

Lacidipine 2 and 4 mg Film-Coated Tablets both meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98). It is therefore justified that the results and conclusions from the bioequivalence study on the 4 mg strength product are extrapolated to the 2 mg strength product.

CLINICAL EFFICACY

No new data on the efficacy have been submitted and none are required for these types of applications.

CLINICAL SAFETY

With the exception of the data collected during the bioequivalence study, no new data have been provided and none are required. No new or unexpected safety issues arose from the bioequivalence study.

SmPC, PIL, LABELS

The SmPCs, PIL and labels are medically acceptable. The SmPCs are consistent with those for the reference products.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM

A summary of the applicant's pharmacovigilance system has been submitted with these applications and is satisfactory.

A suitable Risk Management Plan (RMP) has been provided for these products.

CONCLUSION

The grant of marketing authorisations is recommended for these applications.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Lacidipine 2 and 4 mg Film-Coated 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.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Lacidipine 4 mg Film-Coated Tablets and reference product Motens 4 mg Tablets. As the 2 and 4 mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4 mg strength can be extrapolated to the other strengths of tablet.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the reference products are interchangeable. Extensive clinical experience with lacidipine is considered to have demonstrated the therapeutic value of the compound. The risk/benefit is, therefore, considered to be positive.

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PL 08553/0502 – 0503

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 01 August 2013.
2	Following standard checks and communication with the applicant, the MHRA considered the applications valid on 11 October 2013.
3	Following assessment of the applications, the MHRA requested further information relating to the dossiers on 17 January 2014 and 31 May 2014.
4	The applicant responded to the MHRA's requests, providing further information on 31 March 2014 and 09 July 2014.
5	The applications were approved on 20 August 2014.

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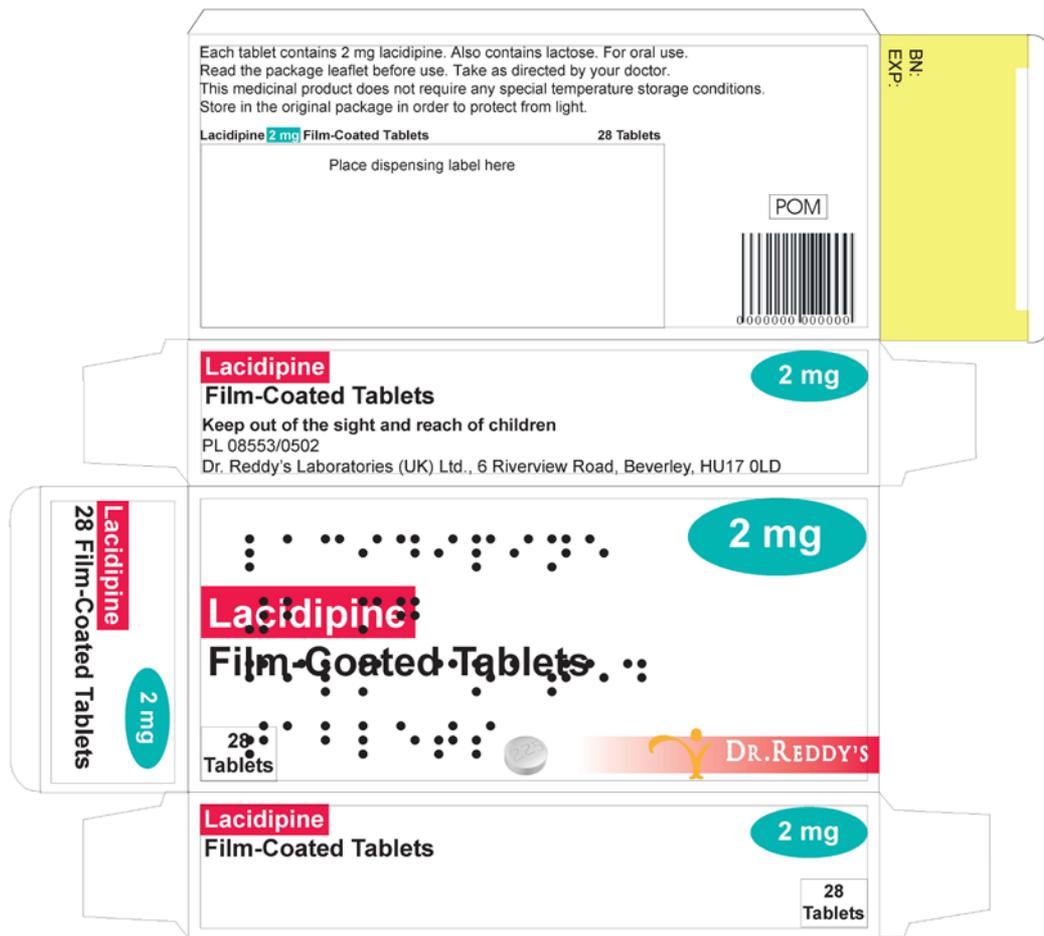
STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics and Patient Information Leaflet

In accordance with Directive 2010/84/EU, the current approved UK versions of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for these products are available on the MHRA website.

Labelling



<p>Monday Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>	<p>Tuesday Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>	<p>Wednesday Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>	<p>Thursday Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>
<p>Friday Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>	<p>Saturday Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>	<p>Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>	<p>Sunday Lacidipine 2 mg Film-Coated Tablets Dr. Reddy's Laboratories (UK) Ltd. Code No. DRUGS/AP/63/96</p>



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