Public Assessment Report

Decentralised Procedure

Amlodipine 1mg/ml Oral Solution
Amlodipine 2mg/ml Oral Solution

Procedure No: UK/H/5543/001-002/DC

UK Licence No: PL 00427/0234-235

Rosemont Pharmaceuticals Limited
LAY SUMMARY

Amlodipine 1mg/ml Oral Solution
Amlodipine 2mg/ml Oral Solution

This is a summary of the Public Assessment Report (PAR) for Amlodipine 1mg/ml and 2mg/ml Oral Solution (PL 00427/0234-235; UK/H/5543/001-002/DC). It explains how the applications for Amlodipine 1mg/ml and 2mg/ml Oral Solution were assessed and their authorisations recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Amlodipine 1mg/ml and 2mg/ml Oral Solution.

For practical information about using Amlodipine 1mg/ml and 2mg/ml Oral Solution, patients should read the package leaflets or contact their doctor or pharmacist.

The products may be referred to as ‘Amlodipine Oral Solution’ in this report.

What is Amlodipine Oral Solution and what is it used for?
Amlodipine Oral Solution is similar to a ‘reference medicine’ already authorised in the UK containing the same active substance, but is available as an oral solution.

The Marketing Authorisation Holder (MAH; Rosemont Pharmaceuticals Limited) has provided its own data to demonstrate the safety and efficacy of Amlodipine Oral Solution regarding this difference from the ‘reference medicine’.

The ‘reference medicine’ for Amlodipine Oral Solution is Istin 10 mg tablets (Pfizer Limited, UK), which was authorised in the UK on 18 September 1989.

Amlodipine Oral Solution is used in children and adolescents (6 to 17 years old) and adults to treat high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is Prinzmetal's or variant angina.

How does Amlodipine Oral Solution work?
Amlodipine Oral Solution contains the active ingredient amlodipine, which belongs to a group of medicines called calcium antagonists.

In patients with high blood pressure, amlodipine works by relaxing blood vessels, so that blood passes through them more easily. In patients with angina, amlodipine works by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. Amlodipine Oral Solution does not provide immediate relief of chest pain from angina.

How is Amlodipine Oral Solution used?
Amlodipine Oral Solution is taken by mouth; it should be taken at the same time each day with a drink of water. This medicine can be used before or after food and drinks.

The bottle should not be shaken before use.

Amlodipine Oral Solution should not be taken with grapefruit juice.

Please read section 3 of the package leaflets for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Amlodipine Oral Solution can only be obtained with a prescription.
What benefits of Amlodipine Oral Solution have been shown in studies?
The MAH has provided studies for Amlodipine Oral Solution to show efficacy for the difference of Amlodipine Oral Solution from the reference product Istin 10 mg tablets (Pfizer Limited, UK). In addition, the MAH (Rosemont Pharmaceuticals Limited) has provided data from the published literature on amlodipine.

What are the possible side effects of Amlodipine Oral Solution?
Like all medicines, Amlodipine Oral Solution can cause side effects although not everybody gets them.

For the full list of all side effects reported with Amlodipine Oral Solution, see section 4 of the package leaflets.

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

Why is Amlodipine Oral Solution approved?
It was concluded that, in accordance with EU requirements, Amlodipine Oral Solution has been shown to have comparable quality and to be comparable to Istin 10 mg tablets (Pfizer Limited, UK). Therefore, the MHRA decided that, as for Istin 10 mg tablets (Pfizer Limited, UK), the benefits outweigh the identified risks and recommended that Amlodipine Oral Solution can be approved for use.

What measures are being taken to ensure the safe and effective use of Amlodipine Oral Solution?
A risk management plan has been developed to ensure that Amlodipine Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflets for Amlodipine Oral Solution, 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 Amlodipine Oral Solution
Germany, France, Ireland and the UK agreed to grant Marketing Authorisations for Amlodipine 1mg/ml and 2mg/ml Oral Solution on 02 February 2015. Marketing Authorisations were granted in the UK on 17 February 2015.

The full PAR for Amlodipine Oral Solution follows this summary.

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

This summary was last updated in April 2015.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>I</th>
<th>Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 6</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>Page 13</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 13</td>
</tr>
</tbody>
</table>

Annex 1 - Table of content of the PAR update for MRP and DCP | Page 14
Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Amlodipine 1mg/ml Oral Solution and Amlodipine 2mg/ml Oral Solution (PL 00427/0234-0245; UK/H/5543/001-002/DC) could be approved. These are prescription-only medicines (POM), which are indicated in children 6 years and over and adults, for the treatment of:

- hypertension;
- chronic stable angina pectoris;
- chronic stable angina pectoris;
- vasospastic (Prinzmetal’s) angina

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, France and Ireland as Concerned Member States (CMS). The applications cross-refer to the reference product Istin 10 mg Tablets (Pfizer Limited, Ireland), which was authorised on 09 August 1989. The corresponding reference product in the UK is Istin 10 mg tablets (PL 00057/0298; Pfizer Limited), which was also authorised in the UK on 09 August 1989.

Amlodipine 1mg/ml and 2 mg/ml Oral Solution contain the active ingredient amlodipine (as amlodipine besilate). Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

One bioequivalence study was submitted to support these applications, comparing the applicant’s test product Amlodipine 2mg/ml oral solution (5ml of 10 mg) with the reference product Istin 10 mg tablets (x1; Pfizer Limited, UK) in healthy subjects under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with International Conference on Harmonisation (ICH) 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 these applications were based on the products being a generic/generic hybrid 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 at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 201) on 02 February 2015. After a subsequent national phase, licences were granted in the UK on 17 February 2015.
II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

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

Each millilitre of Amlodipine 1mg/ml Oral Solution contains 1 milligram of amlodipine (as besilate).

Each millilitre of Amlodipine 2mg/ml Oral Solution contains 2 milligram of amlodipine (as besilate).

The products are clear, pale straw coloured, viscous liquids.

The products also contain glycerol (E422), maltitol liquid (E965) and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in amber (Type III glass) bottles, with high density polyethylene (HDPE), expanded polyethylene (EPE) wadded, child resistant closures. The products are also packaged with a:

1. syringe with a polypropylene (PP) body and purple HDPE plunger with a capacity of 5ml and dosing graduations at every 0.25ml.
2. a low-density polyethylene (LDPE) bottle adaptor.

Amlodipine 1mg/ml and 2mg/ml Oral Solution are available in a pack size of 1 bottle containing 150ml of oral solution.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Amlodipine besilate

INN: Amlodipine besilate
Chemical Name: 3-Ethyl 5-methyl (4RS)-2-[2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate
Molecular Formula: C_{26}H_{31}FClN_{2}O_{8}S
Structure

\[ \text{M}_{r}: \quad 567.1 \]
Appearance: White or almost white powder slightly soluble
Solubility: Freely soluble in methanol, sparingly soluble in anhydrous ethanol, slightly soluble in water and slightly soluble in 2-propanol.

Amlodipine besilate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, amlodipine besilate, are covered by a European Directorate for the Quality of Medicine (EDQM) Certificate of Suitability or by information provided by the Applicant.
II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable, ethanol-free oral solutions containing 1mg/ml and 2mg/ml of amlodipine (as besilate) that were comparable in performance with the reference product Istin 10 mg tablets (Pfizer Limited, UK). Suitable pharmaceutical development data have been provided for these applications.

All the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data have been provided that comply with the release specifications. 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 finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 1 year for the unopened products has been accepted. Once opened, the products should be used within 30 days. The special storage conditions for the products are ‘Store in a refrigerator (2-8°C). Keep the bottle stored upright.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for the applications for Amlodipine 1mg/ml and 2mg/ml Oral Solution.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website. The current labelling is presented below:
Amlodipine 1mg/ml Oral Solution:

Amlodipine 1mg/ml Oral Solution:

Manufactured by the MA Holder:
Rosemont Pharmaceuticals Ltd.

Date opened

Storage: Keep the bottle tight-closed.

See package insert for further information.

Sugar free 150ml

Amlodipine 1mg/ml Oral Solution

Each ml contains 1mg amlodipine besilate.

The product must be used within 28 days of opening.

See package insert for further information.

Manufacturer:

Rosemont Pharmaceuticals Ltd.

London, E37 8EE, UK

UK/H/5543/001-002/DC
Amlodipine 1mg/ml and 2mg/ml Oral solution

III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. 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.

III.2 Pharmacology
Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for generic substitution, at the same or lower amounts, with a product that is already marketed, no increase in environmental exposure to amlodipine is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Amlodipine 1mg/ml and 2mg/ml Oral Solution, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.
The clinical pharmacology of amlodipine is well-known.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted a single-dose bioequivalence study to support the applications, comparing the applicant’s test product Amlodipine 2mg/ml (x 5ml) Oral solution with the reference product Istin 10 mg tablets (x1; Pfizer Limited, UK) in healthy subjects under fasting conditions.

IV.2 Pharmacokinetics
The clinical pharmacokinetic properties of amlodipine are well known. With the exception of data from the bioequivalence study detailed below, no new pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

Study 1
A randomised, single oral dose, open label, two-way, crossover, bioequivalence study comparing the rate and extent of absorption of the test product Amlodipine 2mg/ml oral solution (10 mg in 5ml; Rosemont Pharmaceuticals Limited, UK) with reference product Istin 10 mg tablets (x1; Pfizer Limited, UK) in healthy, adult, human male subjects under fasting conditions.

The subjects were administered a single dose (10 mg as 1 x 5ml oral solution or 1 x10 mg tablet) of either the test product or the reference product with 240 ml of water after at least a
10-hour overnight fast. Blood samples were collected pre-dose and up to 72 hours after each administration. The washout period between the treatment arms was 21 days. The main pharmacokinetic results of the study are summarised in the tables below:

**Summary of Pharmacokinetic results for each treatment**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Comparisons</th>
<th>Ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>Ratio</th>
<th>Lower</th>
<th>Upper</th>
<th>Ratio</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-72}</td>
<td>Test(A) - Reference(B)</td>
<td>103.84</td>
<td>99.50</td>
<td>108.38</td>
<td>7.10</td>
<td>23.88</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AUC_{0-t}</td>
<td>Test(A) - Reference(B)</td>
<td>103.84</td>
<td>99.50</td>
<td>108.38</td>
<td>7.10</td>
<td>23.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max}</td>
<td>Test(A) - Reference(B)</td>
<td>102.66</td>
<td>97.06</td>
<td>108.58</td>
<td>9.34</td>
<td>26.53</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Ratios and confidence intervals

Conclusion of bioequivalence study
The confidence intervals of the test/reference ratio for AUC and C_{max} values lie within the acceptable limits of 80.00% to 125.00%, in line with Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that, following a 10 mg dose, the applicant’s test product Amlodipine 2mg/ml oral solution is bioequivalent to the reference product Istin 10 mg tablet (Pfizer Limited, UK) under fasting conditions.

As the 1mg/ml and 2mg/ml strengths of the product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the results and conclusions of the bioequivalence study of the 2mg/ml strength oral solution can be extrapolated to the 1mg/ml strength oral solution.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of amlodipine are well-known. No new pharmacodynamic data were submitted and none are required for applications of this type.
IV.4 Clinical Efficacy
The clinical efficacy of amlodipine is well-known. No new efficacy data are presented or are required for applications of this type.

IV.5 Clinical Safety
The safety profile of amlodipine is well-known. With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised during the bioequivalence study.

IV.6 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 Amlodipine 1mg/ml and 2mg/ml Oral Solution.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important Identified risks</td>
</tr>
<tr>
<td>• Risk of hypersensitivity reaction to amlodipine or any of the excipients in the Rosemont formulation.</td>
</tr>
<tr>
<td>• Risk of excessive lowering of blood pressure and compromised organ perfusion resulting from prescribing to patients with severe hypotension, shock (including cardiogenic shock), obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis) or haemodynamically unstable heart failure after acute myocardial infarction.</td>
</tr>
<tr>
<td>• Risk of hepatitis, jaundice, or hepatic enzymes increased (cholestasis)</td>
</tr>
</tbody>
</table>

| Important potential risks                      |
| • Medication error – due to incorrect use of or failure to use the dosing spoon or dosing syringe, or confusion by patient, prescriber or pharmacist over the two different available strengths of solution |
| • Overdose – due to medication error or due to ease with which substantial dose can be consumed as a liquid, compared to the same dose as tablets |
| • Off label use particularly in children under 6 years of age |
| • Increased risk of pulmonary oedema, future cardiovascular events and mortality if prescribed in patients with cardiac failure |
| • Risk of ventricular fibrillation and cardiovascular collapse when used with dantrolene infusion especially in presence of hyperkalaemia |
| • Risk of interaction with CYP3A4 inhibitors |

| Important missing information                  |
| • Use in pregnancy                             |
| • Use in children, particularly those under 6 years of age |
| • Use in patients with severe hepatic impairment |

Routine Pharmacovigilance and routine risk minimisation are proposed for all safety concerns. No additional risk minimisation activities were required beyond those included in the product information.
IV.7 Discussion of the clinical aspects
It is recommended that Marketing Authorisations are granted for Amlodipine 1mg/ml and 2mg/ml Oral Solution.

V. USER CONSULTATION
A user consultation with target patient groups on the package information leaflets has been performed on the basis of a bridging report making reference to the PILs for Norvasc (Pfizer Limited, UK), which has been harmonised by the Committee for Medicinal Products for Human use, CHMP) and the applicant’s own user-tested Patient Information Leaflets (PILs) for Clobazam 2mg/ml Oral Suspension and Quetiapine 200mg/5mg Oral Solution. The proposed PILs for Amlodipine Oral Solution have similar format, layout and design as the applicant’s own user-tested PILs. In addition the clobazam product is administered with a dosing syringe, employing similar instructions to that proposed for the Amlodipine Oral Solution leaflets. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Amlodipine 1mg/ml Oral and 2mg/ml Solution 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. As the pharmacokinetics, pharmacodynamics and toxicology of amlodipine are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s test product Amlodipine 2mg/ml oral solution and the reference product Istin 10 mg tablets (Pfizer Limited, UK), following a 10 mg dose, under fasting conditions.

As the 1mg/ml and 2mg/ml strengths of the product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the results and conclusions of the bioequivalence study of the 2mg/ml strength oral solution can be extrapolated to the 1mg/ml strength oral solution.

SAFETY
The safety profile of amlodipine is well-known. With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised during the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PILs and labelling are satisfactory and, where appropriate, in line with current guidance.

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 amlodipine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of Marketing Authorisations is recommended.
## Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
</table>

Y/N (version)