IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Amlodipine Thame 5mg/5ml Oral Solution
Amlodipine Besilate
PA22697/003/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5513/1-2/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 03/10/2018 under procedure number IE/H/0780/1-2/DC].
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/003/001-002
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the applications for Amlodipine Thame 5mg/5ml and 10mg/5ml Oral Solution (PL 39307/0007-0008; UK/H/5513/001-002/DC) could be approved. These are prescription-only medicines (POM), which are indicated for the treatment of:

- hypertension
- 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 Ireland as Concerned Member State (CMS). The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications and cross-refer to the reference products Istin 5 mg and 10 mg tablets (PL 00057/0297-0298; Pfizer Limited, UK), which were authorised in the UK on 18 September 1989.

The active ingredient, amlodipine, is a calcium channel antagonist and belongs to the class dihydropyridines. It acts by inhibiting trans-membrane influx of calcium ions into vascular smooth muscles and cardiac muscles, directly dilating peripheral arterioles and coronary arteries and arterioles.

One bioequivalence study was submitted to support these applications, comparing the applicant's test product Amlodipine 10mg/5ml oral solution (5ml; 10 mg) with the reference product Istin 10 mg tablets (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).

No new non-clinical or other clinical data were submitted, which is acceptable given that these applications were based on the products being generic d medicinal products of originator products that have 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 these products.

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 on 15 July 2015. After a subsequent national phase, licences were granted in the UK on 22 July 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products 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.

The products are clear greenish yellow coloured solutions.

Each 5 ml of Amlodipine Thame 5mg/5ml Oral Solution contains 5mg of amlodipine (as amlodipine besilate) as the active ingredient.

Each 5 ml of Amlodipine Thame 10mg/5ml Oral solution contains 10 mg of amlodipine as amlodipine besilate) as the active ingredient.

The products also contain the pharmaceutical excipients, methyl parahydroxybenzoate (E218), propylene glycol (E1520), anhydrous disodium phosphate (E339), sodium dihydrogen phosphate dihydrate, purified water and glycerol (E422). Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in Type III amber glass bottles, with tamper evident, child resistant polypropylene/polyethylene caps with expanded polyethylene (EPE) liners. The products are packaged with double-ended white polypropylene plastic spoons with 2.5ml and 5ml measuring ends.

Amlodipine Thame Oral Solution is available in pack sizes of 100ml, 150ml and 300ml.

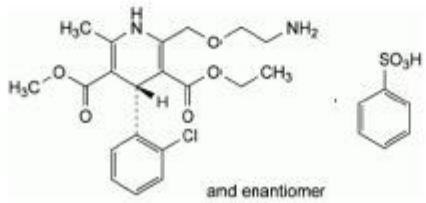
Not all pack sizes may be marketed.

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 (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate
Molecular Formula:	$C_{26}H_{31}FClN_2O_8S$
Structure	



M_r:	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 European Directorate for the Quality of Medicine and Healthcare (EDQM) Certificates of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, oral solutions containing 5mg/5ml and 10mg/5ml of amlodipine (as besilate) that could be considered bioequivalent to the reference products Istin 5 mg and 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. Based on full-scale production and pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

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 9 months for the 5mg/5ml and 10mg/5ml strength unopened products has been accepted, and for the opened products the following shelf-lives have been accepted:

(i) 100ml and 150ml pack size -; Discard after 30 days of first opening
(ii) 300ml pack size: Discard after 60 days of first opening.

The special storage conditions for the products are 'Store in a refrigerator (2°C to 8°C).'

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 Amlodipine Thame 5mg/5ml and 10mg/5ml 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.

III. NON-CLINICAL ASPECTS

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 substitution with products that are 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 Thame 5mg/5ml and 10mg/5ml Oral Solution, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of amlodipine is well-known.

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:

A randomised, open label, two-sequence, two-treatment, two-period, single dose, crossover, single dose, truncated bioequivalence study comparing the rate ad extent of absorption of the test product Amlodipine 10mg/5ml oral solution (Syri limited t/a Thame Laboratories) with reference product Istin 10 mg tablets (Pfizer Limited, UK) in healthy adult human subjects under fasting conditions.

The subjects were administered a single 10 mg dose of either the test product (5ml of 10mg/5ml oral solution) or the reference product (1 x 10 mg) 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 pharmacokinetic results are presented below.

Raw data ranges

PK Parameter	Test Product	Reference Product
C_{max} (ng/mL)	3.52 – 16.83	3.40 – 21.64
AUC_{0-72} (ng.h/mL)	132.36 - 876.52	131.66 – 877.40

AUC_{0-72} area under the plasma concentration-time curve from time zero to72 hours
C_{max} maximum plasma concentration

Arithmetic Means:

PK Parameter	Test product arithmetic mean ± SD	Reference product arithmetic mean ± SD
C_{max} (ng/mL)	5.66 ± 2.89	6.14 ± 3.73
AUC_{0-72} (ng.h/mL)	245.42 ± 148.69	256.44 ± 158.18

AUC_{0-72} area under the plasma concentration-time curve from time zero to72 hours
C_{max} maximum plasma concentration
SD standard deviation

Log-Transformed Geometric Means

PK Parameter	Test Product	Reference Product	% Ratio	90% C.I
C_{max} (ng/mL)	5.24	5.57	94.08	91.75 – 101.73
AUC_t (ng.h/mL)	223.05	230.87	96.61	89.60 – 98.79

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
Ratios and 90% confidence intervals calculated from log-transformed data

Conclusion of the 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**). Hence the test product has been shown to be bioequivalent to the reference Istin 10 mg tablets (Pfizer Limited, UK) under fasting conditions.

The justification for biowaiver for the 5mg/5ml strength of the product can be accepted as the applicant's 5mg/5ml and 10mg/5ml strength oral solutions meet the biowaiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).

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 Thame 5mg/5ml and 10mg/5ml Oral Solution.

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

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Use in patients with severe hypotension • Use in patients with shock • Use in patients with left ventricular outflow tract obstructions • Use in patients with heart failure after acute myocardial infarction • Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (interaction increases amlodipine exposure) • Hepatitis, jaundice, hepatic enzymes increased (cholestasis)
Important potential risks	• Use in patients with hepatic impairment • Increasing the dose in elderly patients • Effect on ability to drive and use machine • 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 • Ventricular fibrillation and cardiovascular collapse when used with dantrolene infusion (especially in presence of hyperkalemia) • Medication error-due to incorrect use of or failure to use the dosing spoon, or confusion by patient, prescriber or pharmacist over the two different available strengths of solution • 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
Missing information	• Use in pregnancy and lactation • Use in children under the age of 6 years • Use in patients with hypertensive crisis

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns, except for overdose and medication error for which the provision of a double ended dosing spoon and child resistant cap are proposed additional risk minimisation measures, as detailed in the table below.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
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	The risks associated with the overdose of the drug product are described in the SPC Section 4.9 and PIL Section 3, and appropriate advice is provided to the prescriber to minimise these risks.	Provision of a double ended dosing spoon and child resistant cap
Medication error – due to incorrect use of or failure to use the dosing spoon, or confusion by patient, prescriber or pharmacist over the two different available strengths of solution	The risk of Medication error – due to incorrect use of or failure to use the dosing spoon, or confusion by patient, prescriber or pharmacist over the two different available strengths of solution is present is minimised under SPC section 4.2 and appropriate advice is provided to the prescriber and user to minimise this risk.	Provision of a double ended dosing spoon

IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Amlodipine Thame 5mg/5ml and 10mg/5ml Oral Solution.

V. USER CONSULTATION

A 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 pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSIONS

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Amlodipine Thame 5mg/5ml and 10mg/5ml Oral 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 10mg/5ml oral solution (Syri Limited t/a Thame Laboratories) and the reference product Istin 10 mg tablets (Pfizer Limited, UK) under fasting conditions.

The justification for biowaiver for the 5mg/5ml strength of the product can be accepted as the applicant's 5mg/5ml and 10mg/5ml strength oral solutions meet the biowaiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**).

SAFETY
The safety profile of amlodipine is well-known. With the exception of the safety data generated during the bioequivalence 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.

VI. REVISION DATE

25/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5513/1-2/DC to IE/H/0780/1-2/DC			