Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Amlodipine 5 mg Tablets
Amlodipine 10 mg Tablets

amlodipine besilate

PL 14251/0267-0268

MANX HEALTHCARE LIMITED

LAY SUMMARY

Amlodipine 5 mg and 10 mg Tablets
amlodipine besilate

This is a summary of the Public Assessment Report (PAR) for Amlodipine 5 mg and 10 mg Tablets. It explains how these products 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 these products.

For practical information about using Amlodipine 5 mg and 10 mg Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Amlodipine 5 mg and 10 mg Tablets and what are they used for?
These products are generic medicines. This means that these medicines are the same as, and considered interchangeable with, reference medicines already authorised, called Istin 5 mg and 10 mg tablets.

Amlodipine 5 mg and 10 mg Tablets are used 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 do Amlodipine 5 mg and 10 mg Tablets work?
The active ingredient in these medicines – amlodipine - belongs to a group of medicines called calcium antagonists.

In patients with high blood pressure this medicine 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.

This medicine does not provide immediate relief of chest pain from angina.

How are Amlodipine 5 mg and 10 mg Tablets used?
The pharmaceutical form of these medicines is tablets and the route of administration is oral (by mouth). This medicine can be used before or after food and drinks but must not be taken with grapefruit juice. Patients should take this medicine at the same time each day with a drink of water.

The recommended initial dose is 5 mg once daily. The dose can be increased to 10 mg once daily.

For children and adolescents (6 to 17 years old), the recommended usual starting dose is 2.5 mg a day only for hypertension. The maximum recommended dose is 5 mg a day. The 5 mg tablet can be divided into equal doses. It is important to keep taking the tablets, and patients or their carers should not wait until their tablets are finished before seeing their doctor.

For further information on how Amlodipine 5 mg and 10 mg Tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Amlodipine 5 mg and 10 mg Tablets have been shown in studies?
Because Amlodipine 5 mg and 10 mg Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Amlodipine 5 mg and 10 mg Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Amlodipine 5 mg and 10 mg Tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

Why were Amlodipine 5 mg and 10 mg Tablets approved?
It was concluded that, Amlodipine 5 mg and 10 mg Tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, 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 Amlodipine 5 mg and 10 mg Tablets?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Amlodipine 5 mg and 10 mg Tablets. The RMP details the important risks of Amlodipine 5 mg and 10 mg Tablets, how these risks can be minimised, any uncertainties about Amlodipine 5 mg and 10 mg Tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Amlodipine 5 mg and 10 mg Tablets:

Summary of safety concerns	
Important identified risks	Pulmonary Oedema
	Use in patients with impaired hepatic function
	Risk of cardiovascular events
	Drug interaction with CYP3A4 inhibitors
Important potential risks	Use in elderly patients
	Breast cancer
Missing information	Use in pregnancy and lactation
	Use in paediatric patients under 6 years old
	Effect on male fertility
	Use in hypertensive crisis

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by

healthcare professionals and patients. Side effects of Amlodipine 5 mg and 10 mg Tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Amlodipine 5 mg and 10 mg Tablets
Marketing Authorisations for Amlodipine 5 mg and 10 mg Tablets were granted in the United Kingdom (UK) on 27 September 2023.

The full PAR for Amlodipine 5 mg and 10 mg Tablets follows this summary.

This summary was last updated in December 2023.

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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) considered that the applications for Amlodipine 5 mg and 10 mg Tablets (PL 14251/0267-0268) could be approved.

The products are approved for the treatment of the following:

- hypertension in adults, adolescents and children aged 6 years or older
- chronic stable angina pectoris in adults
- vasospastic (Prinzmetal's) angina in adults

The active ingredient in Amlodipine 5 mg and 10 mg Tablets is 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.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Istin 5 mg and 10 mg tablets that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. 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 (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing Authorisations for Amlodipine 5 mg and 10 mg Tablets were granted in the United Kingdom (UK) on 27 September 2023.

II QUALITY ASPECTS

II.1 Introduction

These products consist of either 5 mg or 10 mg of amlodipine (as besilate).

In addition to amlodipine besilate, these products also contain the excipients microcrystalline cellulose, calcium hydrogen phosphate (anhydrous), sodium starch glycolate (type A), magnesium stearate and colloidal anhydrous silica.

The finished products are packaged in white opaque PVC/PVDC/Aluminium blisters in pack sizes of 28 tablets.

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

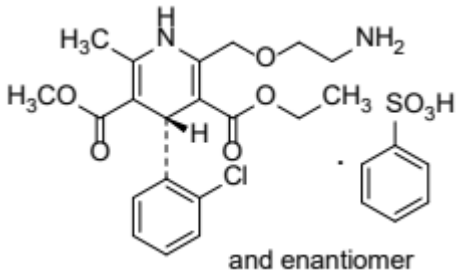
II.2 ACTIVE SUBSTANCE

rINN: amlodipine besilate

Chemical Name: 3-Ethyl 5-methyl(4RS)-2-[(2- aminoethoxy)methyl]-4-(2-chlorophenyl)-6- methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate.
3,5-Pyridinedicarboxylic acid, 2-[(2- aminoethoxy)methyl]- 4-(2-chlorophenyl)- 1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate.
3-Ethyl 5-methyl (±)-2-[(2- aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4- dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate.

Molecular Formula: $C_{26}H_{31}ClN_2O_8S$

Chemical Structure:



Molecular Weight: 567.1

Appearance: White or almost white powder.

Solubility: Slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol, 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 are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

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

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions 'This medicinal product does not require any special temperature storage condition. Store in the original package to protect from light', is acceptable.

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

The grant of marketing authorisations was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine besilate 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.

III.2 Pharmacology

No new pharmacology data were provided, and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided, and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification was provided for non-submission of an Environmental Risk Assessment. As the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated following approval of the marketing authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of amlodipine besilate are well-known. With the exception of data from study C1B00381, no new clinical data were provided or are required for this type of application. An overview based on a literature review and a review of these study is, thus, satisfactory.

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

<u>Bioequivalence study (C1B00381): single dose, fasted.</u>
This study was an open-label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing the test product Amlodipine 10 mg tablets versus the reference product Norvasc 10 mg tablets in healthy adult subjects under fasted conditions.

After an overnight fast of at least 10 hours, subjects were administered a single dose of either the test or the reference product. Blood samples were taken pre-dose and up to 72 hours post dose, with a washout period of 23 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/mL)	26	6.348	26	6.151	103.21
AUC72 (ng/mL)*(hr)	26	247.840	26	244.321	101.44
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria**		**Outcome of BE result**
Cmax (ng/mL)	(98.02%; 108.67%)		80.00% - 125.00%		Bioequivalent
AUC72 (ng/mL)*(hr)	(98.00%; 105.00%)		80.00% - 125.00%		

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test

product and the reference product.
As the additional 5 mg strength of the product meets the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the 10 mg product strength can be extrapolated to the other strengths.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted for these applications and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with these applications and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications. The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**