COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amlodipine ARX 5 mg and 10 mg, tablets

(amlodipine besilate)

NL/H/4678/001-002/DC

Date: 9 January 2020

This module reflects the scientific discussion for the approval of Amlodipine ARX 5 mg and 10 mg, tablets. The procedure was finalised at 16 October 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amlodipine ARX 5 mg and 10 mg, tablets, from Amarox Limited.

The product is indicated for:

- Hypertension
- Chronic stable angina pectoris
- Vasospastic (Prinzmetal's) angina

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Istin 5 mg and 10 mg tablets which has been registered in the United Kingdom by Pfizer Limited UK since 1989. In the Netherlands, the originator product is registered under the name Norvasc 5 mg and 10 mg tablets since 13 June 1990 by Pfizer B.V.

The concerned member states (CMS) involved in this procedure were Germany, Spain, Italy and Sweden

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Amlodipine ARX are white to off white round shaped, biconvex tablets debossed with 'J' on one side and '5' or '10' on the other side. The tablets contain amlodipine besilate equivalent to 5 mg or 10 mg amlodipine.

The tablets are packed in white opaque Alu-PVC/PVdC blisters.

The excipients are: cellulose microcrystalline (E460), silica colloidal anhydrous (E551) and magnesium stearate (E470b)

II.2 Drug Substance

The active substance is amlodipine besilate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is white or almost white powder

and is freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in water and in 2-propanol. Polymorphism has not been described.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is in line with the Ph. Eur. and CEP with additional requirements for particle size distribution and microbiological examination. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches analysed by the drug substance manufacturer, as well as two full-scale batches analysed by the drug product manufacturer.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained.

A bioequivalence study has been performed using the 10 mg tablets. The biobatch used in the bioequivalence study is a representative batch for the drug product. The proposed dissolution method and limit for dissolution is accepted. The *in vitro* dissolution data in support of the biowaiver is acceptable and support the proposed biowaiver of the 5 mg strength.

Manufacturing process

The manufacturing process consists of sifting, blending, lubrication and compression. It has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional

manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
Adequate control specifications, in line with the Ph. Eur. requirements, are applied. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, water content, uniformity of dosage units, dissolution, related substances, assay and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scale batches for each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three commercial scaled of each strength batches stored at 25 °C/60% RH (36 months) and 40 °C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging. In all conditions, the drug products remained stable throughout the full duration, only slight increases in water content and related substances were observed. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: 'Do not store above 30°C. Store in the original packaging to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Amlodipine ARX has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amlodipine ARX 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Istin which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amlodipine besilate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Amlodipine ARX 10 mg, tablets (Amarox Limited, UK) is compared with the pharmacokinetic profile of the reference product Istin 5 mg tablets (Pfizer Limited UK, UK).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver for the lowest strength can be granted based on the following criteria:

- the pharmaceutical products are manufactured by the same manufacturing process
- the qualitative composition of the different strengths is the same
- the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipients to the amount of active substance is the same for all strengths
- appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects. Each subject received a single dose (10 mg) of one of the 2 amlodipine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 24 days.

Blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 20, 24, 30, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable.

Amlodipine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects were withdrawn from the study on medical grounds, two subjects withdrew on their own accord and one subject was withdrawn due to an adverse event (emesis). Therefore, a total of 21 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of S-amlodipine under fasted conditions.

Treatment N=21	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	160 ± 28	--	3.8 ± 0.8	8 (5 - 13)

Reference	159 ± 33	--	3.8 ± 0.7	9 (5 - 12)
***Ratio (90% CI)**	1.01 (0.97 – 1.05)	--	1.00 (0.96 – 1.05)	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-72}** area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**In-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of R-amlodipine under fasted conditions.

Treatment N=21	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	94 ± 18	--	2.5 ± 0.5	8 (5 – 13)
Reference	95 ± 25	--	2.5 ± 0.6	8 (5 – 12)
***Ratio (90% CI)**	1.00 (0.96 – 1.05)	--	1.01 (0.96 – 1.06)	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-72}** area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Amlodipine ARX is considered bioequivalent with Istin.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 ARX.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Istin. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to:

- Amlodipine 5 mg and 10 mg tablets for key safety messages
- Levetiracetam Hetero 750 mg film-coated tablets for design and lay-out

The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amlodipine ARX 5 mg and 10 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Istin 5 mg and 10 mg tablets. Istin is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amlodipine ARX with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 October 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse