LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Amlodipin Medical Valley (amlodipine besilate)

SE/H/1781/01-02/DC

This module reflects the scientific discussion for the approval of Amlodipin Medical Valley. The procedure was finalised on 2019-02-27 For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Amlodipine 5 mg and 10 mg tablets, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medical Valley, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Denmark and Iceland as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Istin 10 mg tablets authorised in United Kingdom since 1989, with Pfizer as marketing authorisation holder.

The reference product used in the bioequivalence study is Istin (Amlodipine besilate) 10 mg tablets, from United Kingdom with Pfizer as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one pivotal bioequivalence study comparing Amlodipine Medical Valley, 10 mg, tablet with the reference product Istin, 10 mg, tablet.

The applicant has conducted a previous bioequivalence study with the same formulation as the product applied for. Since the previous bioequivalence study (Study ID: 30068) was conducted in 2003, i.e. before the Guideline on bioanalytical method validation came into effect, the applicant conducted a new pivotal study. The results in the previous study indicate that for AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Pharmacokinetic properties of the active substance
Absorption: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%.

The bioavailability of amlodipine is not affected by food intake, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of amlodipine is linear within the dose range 5-10 mg.

Elimination: The terminal half-life is 35-50 hours.

Bioequivalence study
Methods
The study was performed at Manipal AcuNova KH Clinical Research Centre, India. The study was conducted between 14 DEC 2015 and 18 JAN 2016. This was a single-dose, two-way crossover study conducted in 24 healthy volunteers (21 completed), comparing amlodipine, 10 mg, tablet with Istin, 10 mg, tablet under fasting conditions. Blood samples for concentration analyses were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of amlodipine were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72h} and C_{max}.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for substance, n=21.

Treatment	AUC_{0-72h} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**366179.79 ± 86137.32**	**9825.51 ± 2650.40**	**6.50 (5.00-11.50)**
Reference	**345718.63 ± 96499.54**	**9061.48 ± 2239.07**	**6.00 (3.00-10.50)**
***Ratio (90% CI)**	**106.06 (96.90-116.09)**	**107.74 (101.72-114.12)**	**-**

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-72h} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 5 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 5 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of amlodipine is linear between 5 mg and 10 mg.

Based on the submitted bioequivalence study, Amlodipine Medical Valley, 10 mg, tablet is considered bioequivalent with Istin, 10 mg, tablet.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Medical Valley.

Safety specification

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 • Effect on male fertility
Missing information	• Use in pregnancy and lactation • Use in paediatric patients under 6 years of age • Use in hypertensive crisis

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 07 January 2019 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the product Amlodipine Ratiopharm 5 and 10 mg tablets (for the content) and to the product Candesartan cilexetil (for the layout).

The user test of the Amlodipine Ratiopharm leaflet was assessed and accepted in the procedure NL/H/881/01-02/MR. The user test for Candesartan cilexetil was assessed and accepted in the procedure NL/H/2046+2047+2048+2270/002-004/DC, NL/H/2391/001-003/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Amlodipine Medical Valley, is found adequate. There are no objections to approval of Amlodipine Medical Valley, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Amlodipine Medical Valley 5 mg and 10 mg tablets was positively finalised on 2019-02-27.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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