LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Amlodipin Aurobindo
(amlodipine besilate)

SE/H/1114/03/DC

This module reflects the scientific discussion for the approval of Amlodipin Aurobindo. The procedure was finalised on 2022-03-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Amlodipin Aurobindo, 7,5 mg, Tablet.

The active substance is amlodipine besilate. A comprehensive description of the indication and posology is given in the SmPC.

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

The application is an extension, addition of a new strength, of the previously authorised product Amlodipin Aurobindo, 5mg, 10mg, tablet marketed by Aurobindo Pharma (Malta) Limited since 2009.

The application for Amlodipin Aurobindo, 7,5 mg, tablet, is a hybrid application made according to Article 10(3) of Directive 2001/83/EC. The applicant, Aurobindo Pharma (Malta) Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Norvasc, 10 mg, tablet authorised in SE since 1991, with Pfizer AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Norvasc, 10 mg, tablet from PT with Pfizer Laboratories Lda as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine, are well known. As Amlodipin Aurobindo is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Conclusions on studies:
Applicant has presented a table showing "IMS Midas Data view for Amlodipine Aurobindo 7.5 mg tablets sale in different countries of EU for the last four years". The sale of this product has not increased significantly over the past four-five years and the active substance is already available in the CMS.

The use of this generic substance will not alter the concentration or distribution of the substance in the environment. Therefore, Amlodipine besylate is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted one single-dose bioequivalence study conducted with the 10 mg strength under fasting conditions.

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. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of amlodipine is linear within the therapeutic dose range.

Elimination: The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing.

Study 498-14
Methods
This was a single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Amlodipine Besilate, 10 mg, tablet with Norvasc, 10 mg, tablet, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of amlodipine were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 16/06/15 and 11/07/15.

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 amlodipine, n=29.

Treatment	AUC_{0-72} pg*h/ml	C_{max} pg/ml	t_{max} h
Test	**354604 ± 74894**	**8408 ± 1884**	**7.00 (5.00-11.00)**
Reference	**359426 ± 79380**	**8593 ± 1876**	**7.00 (4.00-11.00)**
***Ratio (90% CI)**	**98.67 (95.86-101.56)**	**97.88 (94.85-101.00)**	**-**

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 plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-72} 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 applied strength of 7.5 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 method was adequately validated.

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

Absence of studies with the new strength of 7.5 mg is acceptable, as all conditions for biowaiver for additional strength(s), 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 within the therapeutic dose range.

Pharmacodynamics
The MAH has provided a short summary of the literature concerning the known pharmacodynamic profile of amlodipine. No specific information is provided for the 7.5 mg strength. For the sake of conciseness, the summary is therefore not included.
The pharmacodynamic profile of 7.5 mg amlodipine is considered possible to intrapolate from the approved strengths, 5 and 10 mg. No further actions are warranted.

Clinical efficacy
The MAH has provided summaries of 10 scientific articles on the efficacy of amlodipine treatment in subjects with hypertension, six publications concerning the approved indication Chronic stable angina pectoris with the approved posology 5-10 mg amlodipine and one publication concerning Vasospastic angina (please refer to the Clinical AR for the summaries).
The level of details was as expected for data from the literature. The amlodipine treated study population varied from 7 to approximately 500 subjects, most of the studies comprising of 20-100 subjects. Some studies were more than 20 years old and therefore not completely up to date. No study was performed with 7.5 mg amlodipine as a prespecified dose.
The MAH has not clarified how the referred articles were selected, which is considered a weakness of the MAH's clinical overview, as a bias in selection of the articles could not be excluded.
Notwithstanding, as discussed below, the proposed indications are already approved for the 5 mg and 10 mg strengths. This is therefore not pursued.

On 2 February 2011, Pfizer Limited presented to the European Medicines Agency a referral under Article 30 of Directive 2001/83/EC, EMEA/H/A-30/1288, in order to harmonise the national Summary of product characteristics, labelling and package leaflet of the reference product Norvasc/Istin in all EU member states. In this procedure, the indications Hypertension, Chronic stable angina pectoris, and Vasospastic (Prinzmetal's) angina were agreed. The outcome of the referral was implemented to the SmPC of Amlodipin Aurobindo, tablets 5 mg and 10 mg in January 2012.
No other amendments to the common SmPC of Amlodipin Aurobindo apart from the amendment of the 7.5 mg strength is proposed.

At the time of the referral, the CHMP summarised the support for each indication as follows:

- Efficacy in mild to moderate **hypertension** was originally evaluated in 18 placebo/active comparator-controlled studies. The results of the placebo-controlled studies demonstrated that once daily amlodipine is an effective treatment in mild to moderate hypertension, allowing 24-hour control. Other studies indicated that amlodipine reduces blood pressure to the same extent as standard comparative agents, is effective in combination with other agents, and that long-term tolerance does not occur. The data from the relevant clinical studies support this indication.
- Fourteen studies provided data on the efficacy of amlodipine as a **treatment of exertional angina**. Amlodipine treatment resulted in decreased angina, compared to placebo in all placebo-controlled studies but one study. In some studies, but not all, there were statistically significant differences in treatment related changes in exercise times, in favour of amlodipine.
- The specific indication for **vasospastic (Prinzmetal's) angina** was based on a 4-week multicentre, randomised, double-blind, placebo-controlled study to assess the safety and efficacy of amlodipine 10 mg (once daily). It was concluded that amlodipine 10 mg administered once-daily resulted in a statistically significant reduction of angina attack frequency and was safe to use in patients with vasospastic angina pectoris.

Even though only the 10 mg dose had been studied for Vasospastic angina, no specific posology was recommended for this indication in the harmonised SmPC for Norvasc, which also applies for Amlodipine Aurobindo.

The following posology is approved for Amlodipine Aurobindo 5 mg and 10 mg.
Adults:
For both hypertension and angina, the usual initial dose is 5 mg Amlodipine Aurobindo once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.
[…]
Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in paediatric patient's ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients

The proposed posology is considered to support the use of 7.5 mg amlodipin also for the treatment of Vasospastic angina.
In summary, amlodipin is approved for the treatment of Hypertension, Chronic stable angina pectoris, and Vasospastic (Prinzmetal's) angina. The use of amlodipin for these indications has been supported by several clinical studies and extensive postmarketing exposure. The approved posology for all three indications in adults recommends a starting dose of 5 mg with possibility to dose adjustment to 10 mg. It is therefore considered adequately supported that Amlodipine Aurobindo 7.5 mg may be used as an effective treatment in subjects with insufficient effect of 5 mg amlodipine but not in need of the maximum dose of 10 mg.

Clinical safety
The MAH has provided safety data from clinical studies with the reference product Norvasc and post-marketing data from some published studies. These data are not specific for the 7.5 mg dosing.

For the sake of conciseness, the information provided by the MAH has therefore not been included in the AR nor in the overview.

The safety profile of amlodipine is considered well known with an exposure of over 45 million patient years worldwide since the launch of the reference product in the end of the 1980's. No specific safety data was provided for the 7.5 mg strength. However, as there is an extensive post-marketing exposure to amlodipin 10 mg, this is accepted.

Based on the well-known safety profile of the already approved products containing amlodipine 10 mg, no new and unexpected safety issues are expected with Amlodipine Aurobindo 7.5 mg. No further actions are considered warranted.

Risk Management Plan
The MAH has submitted a risk management plan (version 5.0; final sign off 25 Feb 2021), 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 Aurobindo.

Safety specification
No amendments are proposed to the Summary of safety specification (RMP version 4.0; final sign off 02 June 2020), approved in procedure SE/H/1114/001-002/MR.

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

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 5.0, signed 25 Feb 2021 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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Amlohexal 5 mg, 7.5 mg and 10 mg, Procedure No: DK/H/960/001-003/MR (content).
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, Amlodipin Aurobindo, is found adequate. There are no objections to approval of Amlodipin Aurobindo, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. Absence of studies with the new strength of 7.5 mg is acceptable, as all conditions for biowaiver for additional strength are fulfilled and since the pharmacokinetics of amlodipine is linear within the therapeutic dose range. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Amlodipin Aurobindo, 7,5 mg, Tablet was positively finalised on 2022-03-22.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	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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