LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Amlodipin Orion
# (amlodipine besilate)

# SE/H/1684/01-02/DC

**This module reflects the scientific discussion for the approval of Amlodipin Orion. The procedure was finalised on 2017-11-01. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

The application for Amlodipin Orion, 5 mg and 10 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and FI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Norvasc, tablet, 5 mg authorised in Sweden since 1991, with Pfizer AB as marketing authorisation holder.
The reference product used in the bioequivalence study is Norvasc, tablet, 10 mg from Portugal with Pfizer Laboratories Lda 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 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 application, the applicant has submitted the results from one single-dose bioequivalence study conducted with the 10 mg strength under fasting conditions (study code 498-14). In addition to this, the applicant has clarified that an additional bioequivalence study with the to-be-marketed formulation was conducted earlier in 2005 (study Aml-04/05). The new study (study 498-14) was conducted to comply with the current EU-guidelines and is thus pivotal. Study Aml-04/05 is considered supportive.

Study 498-14 (pivotal)
This was a one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Amlodipin Orion, 10 mg, tablet with Norvasc, 10 mg, tablet under fasting conditions. The study was conducted at AXIS Clinical Ltd, Hyderabad, India between 16/05/15 and 11/07/15. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of amlodipine were determined with an adequately validated LC/MS/MS method. 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% (Table 1).

*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** | **354603±74894** | **8408±1883** | **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 h<br>**$C_{max}$** maximum plasma concentration<br>**$t_{max}$** time for maximum plasma concentration | | | |

**calculated based on ln-transformed data*

Bioequivalence was demonstrated.

Study Aml-04/05 (supportive)
The pharmacokinetic profiles of the test and the reference formulations were compared in a 2-way crossover single dose bioequivalence study comprising a total of 24+2 healthy male volunteers.
The clinical phase of the study was performed, the 14th of September 2005 until the 19th of October 2005, at the Clinical Unit, APL Research Centre, Hyderabad, India. Amlodipine in plasma was determined with a validated mass spectrometric method at the Bioanalytical Unit, APL Research Centre, Hyderabad, India. Bioequivalence, in terms of rate and extent of exposure, was adequately demonstrated.

Biowaiver
Absence of studies with the additional strength of 5 mg is acceptable as the pharmacokinetics of amlodipine is linear within the therapeutic dose range and since all biowaiver criteria are fulfilled.

Conclusion
The pharmacokinetic documentation is sufficient.

## 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 (version 1.1, dated May 15, 2017) 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 Orion.

Safety specification
The summary table of safety concerns in RMP version 1.1 is found below.

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Risk of cardiovascular events<br>Hepatic impairment<br>Pulmonary oedema |
| Important potential risks | Drug interaction with CYP3A4 inhibitors<br>Drug interaction with CYP3A4 inducers |
| Missing information | Effect on male fertility<br>Use in pregnancy and breast-feeding<br>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 RMP is approved

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 (PIL) has been performed on the basis of a bridging report making reference regarding *content* to Amlodipin Aurobindo SE/H/1114/01-02/MR).
The layout of the leaflet for Amlodipin Orion will follow a standard Orion layout which has been tested and found appropriate in several user tests.
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, product name, is found adequate. There are no objections to approval of product name, 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 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 Amlodipin Orion, 5 mg and 10 mg, tablet was positively finalised on 2017-11-01.

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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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