LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Amlodipin/Valsartan Teva
(amlodipine besilate, valsartan)

SE/H/2143/01-03/DC

This module reflects the scientific discussion for the approval of Amlodipin/Valsartan Teva. The procedure was finalised on 2022-04-19. 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/Valsartan Teva, 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, Film-coated tablet.

The active substance is amlodipine, amlodipine besilate, valsartan. 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 for Amlodipin/Valsartan Teva, 5mg/80mg, 5mg/160mg, 10mg/160mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Teva BV, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FR, NL, PT (strength 01) and FR, LT, NL, PT (strengths 02-03) as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Exforge, film-coated tablet, 5mg/80mg, 5mg/160mg and 10mg/160mg respectively, authorised in European Union since 2007, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the bioequivalence studies is Exforge, 10 mg/160 mg, film-coated tablet, sourced from Germany, with Novartis Europharm Limited 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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine and valsartan are well known. As amlodipine and valsartan are a widely used, well-known active substances, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Amlodipin/Valsartan Teva is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Amlodipin/Valsartan Teva from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
The results from one pivotal bioequivalence study comparing Amlodipin/Valsartan Teva with the reference product Exforge were submitted with the application.

Pharmacokinetic properties of the active substances

Amlodipine
Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion. The reference product Exforge may be administered with or without food.

Elimination: Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours.

Valsartan
Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect. The reference product Exforge may be administered with or without food.

Elimination: The half-life of valsartan is 6 hours.

Linearity: Amlodipine and valsartan exhibit linear pharmacokinetics.

Study 3154/13
Methods
The pivotal study 3154/13 was a single-dose, two-treatment, three-period, three-sequence, semi-

replicated crossover study conducted in 78 healthy volunteers, comparing Amlodipine/Valsartan, 10 mg/160 mg, film-coated tablet with Exforge, 10 mg/160 mg, film-coated tablet under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of amlodipine and valsartan were determined with LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-tranformed data for AUC and C_{max}. The study was conducted between 30 June 2014 and 18 Aug 2014.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 and 2 below.

Table 1. Amlodipine pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test n=71	**298.7 ± 64.8**	**7.4 ± 1.4**	**8.0 4.5-12.0**
Reference 1 n=72	**299.9 ± 67.3**	**7.3 ± 1.4**	**8.5 3.5-12.0**
Reference 2 n=66	**297.2 ± 68.0****	**7.4 ± 1.3**	**7.5 4.5-12.0**
Reference intra-subject variability (CV%)	**9.03**	**12.21**	**-**
***Ratio (90% CI)**	**100.83 (98.71-103.00)**	**101.24 (98.57-103.98)**	**-**

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*
***n=65*

Table 2. Valsartan pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test n=71	**34.2 ± 13.3**	**5.7 ± 2.4**	**3.5 1.5-6.5**
Reference 1 n=72	**33.6 ± 14.6**	**5.5 ± 2.2**	**3.25 1.5-4.5**
Reference 2 n=66	**35.2 ± 14.7**	**5.6 ± 2.0**	**3.75 1.5-5.0**
Reference intra-subject variability (CV%)	**22.43**	**24.62**	**-**
***Ratio (90% CI)**	**101.98 (96.69-107.57)**	**103.46 (97.46-109.84)**	**-**

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

**calculated based on ln-transformed data*

For amlodipine and valsartan AUC 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 strengths of 5 mg/80 mg and 5 mg/160 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 strengths of 5 mg/80 mg and 5 mg/160 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. Conductance of the study with the highest strength is adequate as the pharmacokinetics of both amlodipine and valsartan is linear within the therapeutic dose range.

Based on the submitted bioequivalence study, Amlodipin/Valsartan Teva is considered bioequivalent with Exforge.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Amlodipin/Valsartan Teva.

Safety specification

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: Summary of Safety Concerns

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

There are no safety concerns recognised for Amlodipine/Valsartan.

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 4.0 signed 2021-03-23 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

The user test has been assessed and accepted.
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet 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 generic product, Amlodipin/Valsartan Teva, is found adequate. There are no objections to approval of Amlodipin/Valsartan Teva, 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/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/Valsartan Teva, 5 mg/80 mg, 5 mg/160 mg, 10 mg/160 mg, Film-coated tablet was positively finalised on 2022-04-19.

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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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