Public Assessment Report

Scientific discussion

Amlodipine/Valsartan Apotex
5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg,
film-coated tablets

(amlodipine besilate/valsartan)

NL/H/3447/001-003/DC

Date: 13 January 2017

This module reflects the scientific discussion for the approval of Amlodipine/Valsartan Apotex 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets. The procedure was finalised on 22 January 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.
## List of abbreviations

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<tr>
<td>RH</td>
<td>Relative Humidity</td>
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<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Amlodipine/Valsartan Apotex 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets from Apotex Europe B.V.

The product is indicated for the treatment of essential hypertension.

Amlodipine/Valsartan tablets is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

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 Exforge which has been registered in the EEA by Novartis Europharm Limited since 19 January 2007 through centralised procedure EMEA/H/C/000716.

The concerned member states (CMS) involved in this procedure were Belgium (all strengths), Luxembourg (all strengths) and Spain (only 5 mg/160 mg and 10 mg/160 mg strengths).

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

II. QUALITY ASPECTS

II.1 Introduction

Amlodipine/Valsartan Apotex is a film-coated tablet in three strengths:

5 mg/80 mg - yellow coloured, round shaped, bevel edged, film-coated tablets with ‘APO’ engraved on one side and ‘5’ over ‘80’ on the other side.

5 mg/160 mg - yellow coloured, modified capsule shaped, film-coated tablets with ‘APO’ engraved on one side and ‘5/160’ on the other side.

10 mg/160 mg - light yellow coloured, modified capsule shaped, film-coated tablets with ‘APO’ engraved on one side and ‘10/160’ on the other side.

Each film-coated tablet contains two active substances: 5 mg or 10 mg of amlodipine, as 6.9 mg or 13.9 mg of amlodipine besilate, and 80 mg or 160 mg valsartan.

The product is packed in Alu-PVC/PVDC clear film blisters.

The excipients are:

Tablet core – anhydrous calcium hydrogen phosphate, magnesium aluminometasilicate, cellulose powdered, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.

Tablet coating - hypromellose E5, hydroxypropyl cellulose, macrogol 8000, talc, titanium dioxide, yellow iron oxide and red iron oxide (only for 10 mg/160 mg).

The three tablet strengths are fully dose proportional.

II.2 Drug Substances

Amlodipine besilate
The active substance is amlodipine besilate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to almost white powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besilate exhibits pseudo polymorphism and exists as anhydrous, monohydrate and dehydrated crystalline forms. It is manufactured in the anhydrous crystalline form. Amlodipine besilate has one chiral carbon centre and exists as a racemic mixture with pKa 8.6.
The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

**Manufacturing process**
The manufacturing process comprises four synthetic steps and is adequately described.

**Quality control of drug substance**
The drug substance is controlled in line with the Ph.Eur. with additional tests for residual solvents and particle size and an additional test on methyl/propyl benzene sulfonates to control potential formation of besilate esters. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

**Stability of drug substance**
Stability data on the active substance have been provided for four batches stored at long-term (25°C/60% RH; up to 60 months) and accelerated (40°C/75% RH; up to 6 months) conditions. Based on the data submitted, a retest period could be granted of 5 years when stored protected from light.

### Valsartan

The active substance is valsartan, an established active substance described in the Ph.Eur. The drug substance is a white to off-white hygroscopic powder, practically insoluble in water and freely soluble in methanol and ethanol. The manufacturer produces the (S)-enantiomer. The product corresponds to the almost amorphous form.

The ASMF procedure is used for the valsartan.

**Manufacturing process**
The synthesis of valsartan comprises three steps and is adequately described. In the last step valsartan is crystallised.

**Quality control of drug substance**
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. For enantiomeric purity, related substances, polymorphic identity, tin content and residual solvents an in-house specification is used. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

**Stability of drug substance**
Stability studies were performed in line with ICH guidelines. Data have been provided for three batches stored at long-term (25°C/60% RH; up to 60 months) and accelerated (40°C/75% RH; up to 6 months) conditions. No significant changes have been observed. Based on these results the proposed retest of 5 years, under nitrogen at 15 to 30°C and protected from exposure to moisture is acceptable.

### 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 excipients used are well known and their amounts usual. The objective of the formulation development trials was to develop a formula and manufacturing process to produce tablets similar to the reference product. The objective was achieved by first physical and chemical characterisation of the reference product, including the dissolution profiles. The development has been adequately performed and described.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Amlodipine/valsartan Apotex and reference product, Exforge. The products used in the bioequivalence study are acceptable.
For the lower strengths a biowaiver is requested. The 5 mg/80 mg and 5 mg/160 mg tablets are fully dose proportional film-coated tablets. Comparative dissolution data in three media (0.1N HCl, pH 4.5, pH 6.8) between 10 mg/160 mg tablets and the other two strengths have been provided. The results show that the all three tablet strengths have comparable dissolution characteristics throughout the physiological pH range.

**Manufacturing process**
The manufacturing process comprises standard steps like de-agglomeration of the excipients, pre-blending of the intragranular excipients followed by granulation by roller compaction, lubrication, compression, preparation of the film-coat suspension followed by film-coating. The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. Validation has been performed with the pilot-scale batches. Process validation for full-scale batches will be performed post authorisation.

**Control of excipients**
An in-house specification is applied for magnesium aluminometasilicate, purified water and red iron oxide shade. For the other excipients reference is made to the Ph.Eur. 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 appearance, identification of drug substances, identification of colorants, hardness, water content, dimensions, uniformity of dosage units, dissolution, assay, enantiomeric purity, degradation products, and micro-biological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Except for water content, the proposed shelf-life specifications are identical to the corresponding release specifications.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scale batches per 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 batches of each strength in accordance with European guidelines. The product is stable at long-term (25°C/60% RH for 24 months) and intermediate conditions (30°C/65% RH for 24 months) except for a slight increase in water content. At accelerated conditions (40°C/75% RH for 6 months) a decrease in dissolution and a significant increase of degradation products is observed. The product is not stable at that condition. Based on the provided stability studies, the proposed shelf-life of 2 years and storage condition (not above 30°C) is acceptable. Based on photo-stability studies, it is concluded that the product is photostable and that light protection measures are not necessary.

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/Valsartan Apotex has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

No post-approval commitments were made.
III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amlodipine/Valsartan Apotex 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 Exforge 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 and valsartan are well-known active substances 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Amlodipine/Valsartan Apotex 10 mg/160 mg, film-coated tablets (Apotex Europe B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Exforge 10 mg/160 mg film-coated tablets (Novartis Europharm Limited, United Kingdom).

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH applied for a biowaiver for the lower strengths 5 mg/160 mg and 5 mg/80 mg, based on standard biowaiver for strength criteria.

- For the 3 different strengths, the same manufacturing process and same qualitative composition is applied.
- The quantitative composition of the 5 mg/80 mg strength is fully dose proportional compared to the 10 mg/160 mg strength.
- The quantitative composition of the 5 mg/160 mg strength is not dose proportional compared to the 10 mg/160 mg strength, however this deviation from proportionality is within the exemptions as set out in the Guideline on Bioequivalence, as the amount of active substance is less than 5% of the tablet core weight and the amount of a filler (Anhydrous Calcium Hydrogen Phosphate) is changed to account for the change in amount of active substance.
- Similar dissolution between 10 mg/160 mg biobatch and the 5 mg/80 mg and the 5 mg/160 mg strength has been shown in 0.1 N HCl, pH 4.5 and pH 6.8 media.
The biowaiver for both additional strengths is acceptable.

**Design**

An open-label, single-dose, randomised, two-period, two-sequence, two-treatment, crossover, comparative bioequivalence study was carried out under fasted conditions in 66 healthy male (n=34) and female (n=32) subjects, aged 19-52 years. Each subject received a single dose of one of the 2 formulations of amlodipine (10 mg) and valsartan (160 mg). The tablet was orally administered with 240 ml water. Subjects fasted overnight for at least 10 hours prior to drug administration and for at least 4 hours following drug administration. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples for the first 30 subjects were collected pre-dose and at 0 (x2), 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 24, 30, 36, 48 and 72 hours after administration of the products. All subjects numbered 31 and up underwent the following sampling scheme: 0 (x2), 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 14, 18, 24, 30, 36 and 48 hours after dosing. Data from the first 30 subjects completing the study were used for the analysis of amlodipine; data of all subjects completing the study were used for the analysis of valsartan.

The design of the study is acceptable. For both amlodipine and valsartan, the parent compounds are analysed. Due to the long half life of amlodipine, a washout of 21 days was maintained. It is pre-specified to analyse only the first 30 subjects for amlodipine.

**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**

Three subjects were withdrawn due to adverse events. 29 and 63 subjects were included for the pharmacokinetic analysis of amlodipine and valsartan, respectively.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\text{0-72} (ng.h/ml)</th>
<th>AUC\text{0-∞} (ng.h/ml)</th>
<th>C\text{max} (ng/ml)</th>
<th>t\text{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>267 ± 54</td>
<td>395 ± 117</td>
<td>7.4 ± 1.2</td>
<td>6.0 (5.0 - 16.0)</td>
</tr>
<tr>
<td>Reference</td>
<td>273 ± 56</td>
<td>397 ± 116</td>
<td>7.4 ± 1.2</td>
<td>6.0 (5.0 - 16.0)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.98 (0.94 - 1.01)</td>
<td>0.99 (0.95 - 1.03)</td>
<td>1.00 (0.96 - 1.04)</td>
<td>--</td>
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</table>

*ln-transformed values

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\text{max} (median, range)) of valsartan under fasted conditions.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC\text{0-t} (ng.h/ml)</th>
<th>AUC\text{0-∞} (ng.h/ml)</th>
<th>C\text{max} (ng/ml)</th>
<th>t\text{max} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>30.7 ± 14.1</td>
<td>31.9 ± 14.3</td>
<td>5.0 ± 1.9</td>
<td>3.0 (1.0 - 5.0)</td>
</tr>
<tr>
<td>Reference</td>
<td>27.5 ± 11.6</td>
<td>28.5 ± 11.6</td>
<td>4.6 ± 2.1</td>
<td>3.0 (1.0 - 4.5)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.12 (1.04 - 1.20)</td>
<td>1.13 (1.05 - 1.21)</td>
<td>1.13 (1.04 - 1.23)</td>
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</tr>
</tbody>
</table>
Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC<sub>0-72</sub>, AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Amlodipine/Valsartan Apotex 10 mg/160 mg, film-coated tablets is considered bioequivalent with Exforge 10 mg/160 mg film-coated tablets.

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/Valsartan Apotex.

Summary table of safety concerns as approved in RMP:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>• Fetotoxicity (with use in 2&lt;sup&gt;nd&lt;/sup&gt; or 3&lt;sup&gt;rd&lt;/sup&gt; trimester of pregnancy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Hypotension</td>
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<td></td>
<td>• Hyperkalaemia</td>
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<td></td>
<td>• Decreased renal function</td>
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<td></td>
<td>• Angioedema</td>
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<tr>
<td>Important potential risks</td>
<td>• Teratogenicity (with use during 1&lt;sup&gt;st&lt;/sup&gt; trimester of pregnancy)</td>
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<tr>
<td>Missing information</td>
<td>• Use during breast feeding</td>
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<tr>
<td></td>
<td>• Use in patients who had recent kidney transplantation</td>
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<tr>
<td></td>
<td>• Use in children below 18 years of age</td>
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<td></td>
<td>• Use in hypertensive crisis</td>
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</table>

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 Exforge. 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 the content of the PL of the innovator Exforge. The layout of the PL can be linked to the approved PL of Irbesartan Apotex (NL Licence RVG 106982-4), which is a medicinal product with comparable cardiovascular indication and use. In conclusion, the bridging of the PL contents and lay-out submitted by the MAH has been found acceptable.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amlodipine/valsartan Apotex 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Exforge 5 mg/80 mg, 5 mg/160 mg and 10 mg/160 mg, film-coated tablets. Exforge 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.

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/valsartan Apotex with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 January 2016.
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<tr>
<td>Replacement or addition of a site where batch control/testing takes place</td>
<td>NL/H/3447/I A/001/G</td>
<td>IA</td>
<td>18-8-2016</td>
<td>17-9-2016</td>
<td>Approval</td>
<td>No</td>
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