CBG MEB

Public Assessment Report

Scientific discussion

Olmesartanmedoxomil/Amlodipine STADA 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets

(olmesartan medoxomil/amlodipine besilate)

NL/H/3868/001/DC

Date: 2 November 2018

This module reflects the scientific discussion for the approval of Olmesartanmedoxomil/Amlodipine STADA 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets. The procedure was finalised on 10 August 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Olmesartanmedoxomil/Amlodipine STADA 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets from STADA Arzneimittel AG.

The product is indicated for treatment of essential hypertension.

Olmesartanmedoxomil/Amlodipine STADA is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy (see SmPC sections 4.2 and 5.1).

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 Sevikar 40 mg/10 mg film-coated tablets (NL License RVG 100984) which has been registered in The Netherlands by Daiichi Sankyo Nederland B.V. since 19 August 2008.

The concerned member states (CMS) involved in this procedure were Belgium, Germany, Spain, Ireland, Italy, Luxemburg, Portugal and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Olmesartanmedoxomil/Amlodipine STADA is a round, biconvex, film-coated tablet in three strengths:

- 20 mg/5 mg film-coated tablets are white. Each tablet contains 20 mg of olmesartan medoxomil and 5 mg of amlodipine as 6.935 mg amlodipine besilate.
- 40 mg/5 mg film-coated tablets are yellowish-white. Each tablet contains 40 mg of olmesartan medoxomil and 5 mg of amlodipine as 6.935 mg amlodipine besilate.
- 40 mg/10 mg film-coated tablets are brownish-red. Each tablet contains 40 mg of olmesartan medoxomil and 10 mg of amlodipine as 13.87 mg amlodipine besilate.

The film-coated tablets are packed in oPA-Alu-PVC//Alu blisters.

The excipients are:
Tablet core - microcrystalline cellulose, crospovidone type A, colloidal anhydrous silica, magnesium stearate and lactose monohydrate.
Tablet coat – hydroxypropyl pregelatinised starch, stearic acid, sorbitol (E420), titanium dioxide, iron oxide yellow (only the 40 mg/5 mg strength), and iron oxide red (only the 40 mg/5 mg and 40 mg/10 mg strength).

The cores of the tablet strengths 20 mg/5 mg and 40 mg/10 mg are fully dose proportional. The cores of the tablet strengths 40 mg/5 mg and 40 mg/10 mg are identical except for the amount of 5 mg amlodipine which is corrected with the same amount of filler lactose.

II.2 Drug Substances

Olmesartan medoxomil
The active substance is olmesartan medoxomil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Olmesartan medoxomil is practically insoluble in water, slightly soluble in ethanol (96%), and practically insoluble in heptane. Olmesartan medoxomil does not contain any chiral centre. The MAH has shown that the polymorphic forms of both manufacturers are stable.

The CEP procedure is used for the active substance by both manufacturers. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specification meets the requirements of the monograph in the Ph.Eur. and includes an additional test and requirement for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for two batches from manufacturer-I and three batches from manufacturer-II.

Stability of drug substance
The active substance is stable for two years (manufacturer-I) or one year (manufacturer-II) when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Amlodipine besilate
The active substance is olmesartan medoxomil, an established active substance described in the Ph.Eur. Amlodipine besilate is slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol (96%), slightly soluble in 2-propanol. Amlodipine besilate contains one chiral centre. Both manufacturers have used the CEP procedure. The MAH has shown that the polymorphic forms of both manufacturers are stable.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specification meets the requirements of the monograph in the Ph.Eur. and includes an additional test and requirement for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for four batches from manufacturer-I and one batch from manufacturer-II.

Stability of drug substance
The active substance is stable for five years (both manufacturers) when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of excipients is justified and their functions explained. The drug product can be regarded as standard dosage form. Drug load is approximately 19% for olmesartan medoxomil and approximately 3% and 6% for amlodipine besilate.

Essential similarity of the test product to Sevikar tablets is claimed on the basis of a comparative bioequivalence study carried out using of Olmesartanmedoxomil/Amlodipine 40 mg/10 mg tablets. The choice of the test product batches and the reference batches used in the biostudy is acceptable in view of the batch size, production method and location, and assay values. The dissolution method chosen is sufficiently discriminating for olmesartan medoxomil and for amlodipine. Comparative *in vitro* dissolution results are included, supplementary to the *in vivo* bioequivalence study with the 40 mg/10 mg strength and to support the biowaiver for the 40 mg/5 mg and 20 mg/5 mg strengths.

The provided comparative dissolution profiles are similar for pH 1.0 and pH 4.5 (similarity factor (f2) is more than 50 or >85% dissolved in 15 minutes); for pH 6.8 the dissolution profiles are not similar. These differences are substance related and not formulation related. Hence the MAH performed an additional dissolution study at pH 6.8 to compare the 40 mg/10 mg tablet (one film-coated tablet per vessel) with 40 mg/5 mg (two film-coated tablets per vessel) and 20 mg/5 mg (two film-coated tablets per vessel). The calculated f2-values are above 50, demonstrating that the dissolution profiles are similar and the observed difference is drug substance related rather than formulation related.

Manufacturing process
The manufacturing process is a standard manufacturing process and is described adequately. The drug product is manufactured by dry granulation. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scale batches in accordance with the relevant European guidelines.

Control of excipients
Specifications are provided for the coatings and all other excipients. For all 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, average weight, identification, dissolution, uniformity of dosage units by mass variation, degradation products, assay and microbial quality. Tablet hardness and disintegration are tested on the tablet cores as in process controls which is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six pilot scale batches 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 pilot batches of each strength at 25°C/60% RH (12 months) and 45°C/75% RH (6 months). All results comply with the specification. Tablets were stored in the proposed packaging. On the basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: store in original package in order to protect from moisture. Photostability studies have been performed on one batch. The tablets are not sensitive to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. A TSE declaration for lactose monohydrate has been provided certifying that the milk use for the production of lactose monohydrate is sourced from healthy animals in the same conditions as milk collected for human consumption. The calf rennet is in accordance with the regulatory requirements.

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Olmesartanmedoxomil/Amlodipine STADA has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Olmesartanmedoxomil/Amlodipine STADA 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 Sevikar 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

Olmesartan medoxomil and amlodipine besilate are well-known active substance 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 Olmesartanmedoxomil/Amlodipine STADA 40 mg/10 mg film-coated tablets (STADA Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Sevikar 40 mg/10 mg film-coated tablets (Daiichi-Sankyo, Germany).

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

Biowaiver
A biowaiver is granted for the other strengths based on the following arguments:
- The pharmaceutical products are manufactured by the same manufacturing process,
- The qualitative composition of the different formulations is the same.
- The quantitative composition is dose proportional for the 20 mg/5 mg strength. Also for the 40 mg/5 mg strength this requirement is considered acceptable.
- Linear pharmacokinetics can be applied in the therapeutic dose range.
- Similar dissolution profiles were provided by the MAH at all three pH levels.

Design
A single centre, single dose, randomised, open label, two treatment, two period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-50 years. Each subject received a single dose (40 mg olmesartan and 10 mg amlodipine) of one of the two formulations. There were two dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the bioequivalence study is acceptable and in accordance with the guideline on the investigation of bioequivalence. The washout period of 21 days is long enough. The sampling period is long enough to adequately estimate pharmacokinetic parameters. Also the sampling scheme is adequate to estimate pharmacokinetic parameters.

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
One subject was withdrawn from the study by the investigator due to an adverse event after drug administration (test formulation) in the first treatment period. Therefore, 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan under fasted conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	7008 ± 2064	7346 ± 2192	1013 ± 285	2.25 (1.25 – 5.00)
Reference	7121 ± 1987	7444 ± 2082	1020 ± 271	2.25 (1.25 – 4.00)
***Ratio (90% CI)**	0.98 (0.94 – 1.03)	--	0.99 (0.94 – 1.04)	**--**

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine under fasted conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	198 ± 47	--	5.5 ± 1.2	5.00 (4.50 – 8.00)
Reference	191 ± 45	--	5.3 ± 1.0	5.00 (4.50 – 8.00)
***Ratio (90% CI)**	1.03 (0.99 – 1.08)	--	1.02 (0.98 – 1.07)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Olmesartanmedoxomil/Amlodipine STADA is considered bioequivalent with Sevikar.

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 Olmesartanmedoxomil/Amlodipine STADA.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hyperkalaemia • Hypotension • Foetotoxicity • Sprue-like enteropathy
Important potential risks	• Elevation of liver function values • Renal impairment • Hypersensitivity reactions incl. angioedema and serum sickness • Decrease in haemoglobin and/or haematocrit • CV risks in patients with type 2 diabetes
Missing information	• Exposure in children and adolescents • Exposure during breast feeding

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 Sevikar. 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

The package leaflet has (PL) 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 test consisted of: a pilot test with three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Olmesartanmedoxomil/Amlodipine 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Sevikar 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets. Sevikar 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 Olmesartanmedoxomil/Amlodipine STADA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 August 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3868/IB/001/G	Type IB.B.II.b.1.e, Addition of finished product manufacturer Type IAIN. B.II.b.1.a, Addition of secondary packaging site Type IAIN. B.II.b.1.b, Addition of primary packaging site	--	21-2-2018	Approval	--