COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Olmesartan medoxomil/Amlodipine Sigallata 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg, film-coated tablets

(olmesartan medoxomil/amlodipine besilate)

NL/H/4277/001-003/DC

Date: 9 April 2019

This module reflects the scientific discussion for the approval of Olmesartan medoxomil/Amlodipine Sigallata. The procedure was finalised at 6 December 2018. 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
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Olmesartan medoxomil/Amlodipine Sigallata 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg, film-coated tablets from Sigallata Limited.

The product is indicated for treatment of essential hypertension.

Olmesartan medoxomil/Amlodipine Sigallata is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy (see SmPC section 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 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg film-coated tablets (NL License RVG 100984, 100986, 100987) which has been registered in The Netherlands by Daiichi Sankyo Nederland B.V. since 19 August 2008.

The concerned member state (CMS) involved in this procedure was Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Olmesartan medoxomil/Amlodipine Sigallata is a round, convex, film-coated tablet in three strengths:

- 20 mg/5 mg film-coated tablets are white, debossed with “5” on one side, the other side is scored and debossed with “2” on the left side of the score and “0” on the right side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- 40 mg/5 mg film-coated tablets are yellowish, debossed with “5” on one side, the other side is scored and debossed with “4” on the left side of the score and “0” on the right side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
- 40 mg/10 mg film-coated tablets are brownish-red, debossed with “10” on one side, the other side is scored and debossed with “4” on the left side of the score and “0” on the right side. The tablet can be divided into equal doses.

The product contains as active substances 40 mg or 20 mg of olmesartan medoxomil combined with 10 mg or 5 mg of amlodipine, as 13.87 mg or 6.94 mg amlodipine besilate.

The film-coated tablets are packed in OPA/Aluminium/PE+ desiccant -Aluminium blister.

The excipients are:

Tablet core
- Cellulose microcrystalline
- Lactose monohydrate
- Crospovidone
- Povidone
- Sodium starch glycolate
- Silica, colloidal hydrated
- Magnesium stearate

Film-coating
- Polyvinyl alcohol part-hydrolysed (E1203)
- Macrogol (E1521, polyethylene glycol)
- Talc (E553b)
- Iron oxide red (E172) (40 mg/10 mg film-coated tablets only)
- Titanium dioxide (E171) (20 mg/5 mg, 40 mg/5 mg film-coated tablets only)
- Iron oxide yellow (E172) (40 mg/5 mg film-coated tablets only)

The core tablets of the 40 mg/10 mg and 20 mg/5 mg strengths are dose proportional. The composition of the core tablets of the 40 mg/5 mg strength is identical to that of the 40 mg/10 mg strength with the exception of the lower amlodipine besilate content which is compensated by a higher amount of an excipient to reach the same total weight.

II.2 Drug Substance

Olmesartan medoxomil
The active substance is olmesartan medoxomil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water. Solubility is pH dependent. The active substance exhibits polymorphism. Form A is used for the drug product.

The CEP procedure is used by both manufacturers for the active substance. 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
CEPs have 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 and meets the requirements of the monograph in the Ph.Eur. The CEPs contain additional requirements for identification, impurities, residual solvents, particle size distribution, and bulked and tapped density. Batch analytical data demonstrating compliance with this specification have been provided for one batch of manufacturer-I and three batches of manufacturer-II.

Stability of drug substance
The active substance is stable for five years (manufacturer-I) or three years (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
Amlodipine besilate is an established active substance described in the Ph.Eur. The active substance is slightly soluble in water. The active substance exhibits polymorphism. The anhydrous form is used for the drug product. The CEP procedure is used for the active substance.

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 and meets the requirements of the monograph in the Ph.Eur. The CEPs contain additional requirements for impurities, particle size distribution, and benzene. Batch analytical data demonstrating compliance with this specification have been provided for one batch.

Stability of drug substance
The active substance is stable for five years (manufacturer-I) or three years (manufacturer-II) 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 the excipients

is justified and their function explained. A wet granulation approach was chosen for olmesartan medoxomil and a dry mix approach was chosen for amlodipine besilate. Manufacturing process development has been adequately explained. A test for uniformity of mass for subdivided parts is included in the proposed drug product specification. Although all strengths can be broken into equal halves, division into equal doses is only applicable for the 40 mg/10 mg strength as breaking of the 40 mg/5 mg and 20 mg/5 mg strengths results in doses which are not described in the SmPC of the reference product. For the latter, breaking only for the ease of swallowing is indicated in section 3 of the proposed SmPC.

The development of the routine dissolution method was sufficiently described and acceptable limits for dissolution have been set for both active substances.
Bioequivalence studies were carried out for the 40 mg/10 mg and 40 mg/5 mg strengths. The provided comparative dissolution profiles of the biobatches obtained at pH 1.2, pH 4.5, and pH 6.8 support bioequivalence.
A biowaiver of strength is requested for the 20 mg/5 mg strength. Dissolution profiles of the 40 mg/10 mg and 20 mg/5 mg strengths were compared at pH 1.2, pH 4.5, and pH 6.8. More than 85% of the amlodipine component was dissolved within 15 minutes in all cases. F_2 and bootstrap calculations demonstrated similarity for the olmesartan medoxomil component.

Manufacturing process

The manufacturing process consists of wet granulation of olmesartan medoxomil with excipients followed by fluid bed drying, dry blending of amlodipine besilate with excipients, blending, compression, and coating. The manufacturing process is a standard process. The manufacturing process was adequately described. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two pilot scale batches per strength batches in accordance with the relevant European guidelines.

Control of excipients

Except for the iron oxides present in the film-coating premixes, the excipients and individual components of the film-coating materials are of Ph.Eur. quality. 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 description/appearance, identification, dissolution, uniformity of dosage units by content uniformity, assay, impurities/degradation products, water content, identification of colour agents, uniformity of mass of subdivided parts, and microbiological examination of non-sterile products. The release and shelf life specifications differ with regard to description/appearance and content of specified and total impurities. Identity of the colouring agents is only tested at release. 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 two 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 has been provided on two pilot scale batches of each strength stored at 25°C/60% RH (24 months), and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. No significant changes were seen at both storage conditions.
The proposed shelf-life of two years without any special storage conditions is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is sourced from healthy cows in the same conditions as milk collected for human consumption. 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 Olmesartan medoxomil/Amlodipine Sigallata has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Perform full specification analytical testing in accordance with requirements of GMP Part I, Chapter 5 of every batch of active substance manufactured by a specified manufacturer before use in production of finished product, at a testing laboratory other than the manufacturer.
- In addition to full specification testing, testing for NDMA/NDEA should also be conducted.
- To inform the RMS immediately in case of any out of specification results (OOS) obtained from the analysis performed.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Olmesartan medoxomil/Amlodipine Sigallata 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 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of two strengths of the test product Olmesartan medoxomil/Amlodipine Sigallata 40 mg/10 mg and 40 mg/5 mg (Teva pharmaceuticals Europe B.V., The Netherlands) is compared with the pharmacokinetic profile of the corresponding strength of the reference product Sevikar (Daiichi Sankyo, Germany).

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.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Biowaiver
A biowaiver has been granted for the 20 mg/5 mg strength based on the following:
- The pharmaceutical products are manufactured by the same manufacturing process.
- Qualitative composition of the different formulations is the same.
- Appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.
- The quantitative composition is dose proportional for the 40 mg/10 mg bio strength, and 20/5 mg strength.
- Linear pharmacokinetics applied in the therapeutic dose range.

Bioequivalence studies
Pharmacokinetic study 40 mg/10 mg
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 19-44 years. Each subject received a single dose (40 mg and 10 mg) of one of the 2 olmesartan/amlodipine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 21 days.

Olmesartan blood samples were collected pre-dose and 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products.
Amlodipine blood samples were collected pre-dose and 2.00, 3.00, 4.00, 5.00, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 11.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00 and 72.00 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 and sampling period and scheme are adequate to estimate the pharmacokinetic parameters of interest.

Results
One subject did not report at the study facility at period 2. Another subject was withdrawn as per sponsor's discretion. Two subjects were withdrawn due to a positive breath alcohol test at period 2 admission. Therefore 56 subjects were eligible for pharmacokinetic analysis. For amlodipine only the samples from the first 30 subjects who complete both periods were analysed as per the protocol.

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

Treatment N=30	AUC_{72} (pg.h/ml)	C_{max} (pg/ml)	t_{max} (h)
Test	284800 ± 57380	7230 ± 1328	8.0 (2.0 – 16.0)
Reference	281514 ± 54313	7057 ± 1368	8.0 (3.0 – 12.0)
***Ratio (90% CI)**	1.01 (0.98 – 1.04)	1.03 (0.99 – 1.06)	--
AUC_{72} area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration t_{max} time for maximum concentration			

**ln-transformed values*

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

Treatment N=56	AUC_{72} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	9868 ± 2956	10028 ± 3021	1416 ± 424	2.165 (1.0 – 4.0)
Reference	9566 ± 2982	9723 ± 3057	1326 ± 420	2.330 (1.3 – 6.0)
***Ratio (90% CI)**	1.04 (1.00 – 1.07)	1.04 (1.00 – 1.07)	1.07 (1.02 – 1.13)	--
AUC_{72} area under the plasma concentration-time curve from time zero to 72 hours $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum concentration				

**ln-transformed values*

Pharmacokinetic study 40 mg/5 mg

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 18-44 years. Each subject received a single dose (40 mg and 5 mg) of one of the 2 olmesartan/amlodipine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 22 days.

Olmesartan blood samples were collected pre-dose and 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products.

Amlodipine blood samples were collected pre-dose and 2.00, 3.00, 4.00, 5.00, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 11.00, 12.00, 14.00, 16.00, 24.00, 36.00, 48.00 and 72.00 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 and sampling period and scheme are adequate to estimate the pharmacokinetic parameters of interest.

Results

Two subjects were withdrawn from the study as inclusion criteria were not fulfilled. These subjects were replaced by two other subjects. In addition two subjects did not report to the study facility during period 2, hence withdrawn. Another subject reported an adverse event in period 1 and was withdrawn from the study. Therefore, 41 subjects were eligible for pharmacokinetic analysis. For amlodipine only the samples from the first 30 subjects who complete both periods were analysed as per the protocol.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine under fasted conditions.

Treatment N=30	**AUC_{72} (pg.h/ml)**	**C_{max} (pg/ml)**	**t_{max} (h)**
Test	140271 ± 28909	3691 ± 734	7.25 (5.0 – 12.0)
Reference	139746 ± 32848	3668 ± 815	7.50 (5.0 – 11.0)
***Ratio (90% CI)**	1.01 (0.97 – 1.05)	1.01 (0.98 – 1.04)	--
AUC_{72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan under fasted conditions.

Treatment N=41	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	9229 ± 2796	9399 ± 2830	1278 ± 310	2.00 (1.33 – 4.00)
Reference	8741 ± 2587	8908 ± 2623	1246 ± 344	2.00 (1.00 – 4.00)
***Ratio (90% CI)**	1.05 (1.00 – 1.11)	1.05 (1.00 – 1.11)	1.04 (0.98 – 1.10)	--

$AUC_{0-\infty}$	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 studies

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 studies Olmesartan medoxomil/Amlodipine Sigallata 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 Olmesartan medoxomil/Amlodipine Sigallata.

Table 5. 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

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 Olmesartan medoxomil/Amlodipine Teva. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Olmesartan medoxomil/Amlodipine Sigallata, 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 Olmesartan medoxomil/Amlodipine Sigallata with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 December 2018.

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