CBG MEB

Public Assessment Report

Scientific discussion

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

(olmesartan medoxomil/amlodipine besilate)

NL/H/3725/001-003/DC

Date: 14 May 2018

This module reflects the scientific discussion for the approval of Olmesartan medoxomil/Amlodipine ratiopharm 20 mg/5 mg, 40 mg/5 mg and 40 mg/10 mg, film-coated tablets. The procedure was finalised on 27 September 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

ASMF	Active Substance Master File
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 ratiopharm 20 mg/5 mg, 40 mg/5 mg and 40 mg/10 mg, film-coated tablets from ratiopharm Nederland B.V.

Treatment of essential hypertension
The product is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil or amlodipine monotherapy

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Sevikar 20 mg/5 mg, 40 mg/5 mg and 40 mg/10 mg, film-coated tablets (NL License RVG 100984-100986) which has been registered in the Netherlands by Daiichi Sankyo Netherlands B.V. since 19 August 2008.

A comprehensive description of the indications and posology is given in the SmPC.

The concerned member states (CMS) involved in this procedure were Austria, Germany, Spain and Portugal.

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 ratiopharm 20 mg/5 mg is a white, round standard convex, film-coated tablet, debossed with “5” on one side, the other side of the tablet is scored and debossed with "2" on the left side of the score and "0" on the right side. Each tablet contains 20 mg of olmesartan medoxomil and 5 mg of amlodipine (as amlodipine besilate).
- Olmesartan medoxomil/Amlodipine ratiopharm 40 mg/5 mg is a yellowish, round standard convex, film-coated tablet, debossed with "5" on one side, the other side of the tablet is scored and debossed with "4" on the left side of the score and "0" on the right side. Each tablet contains 40 mg of olmesartan medoxomil and 5 mg of amlodipine (as amlodipine besilate).
- Olmesartan medoxomil/Amlodipine ratiopharm 40 mg/10 mg is a brownish-red, round standard convex, film-coated tablet, debossed with "10" on one side, the other side of the tablet is scored and debossed with "4" on the left side of the score and "0" on the right side. Each tablet contains 40 mg of olmesartan medoxomil and 10 mg of amlodipine (as amlodipine besilate).

The film-coated tablets are packed in OPA/Aluminium/PVC/Aluminium blisters or a HDPE bottle with a polypropylene child resistant closure with a desiccant canister.

The excipients are:
tablet core - cellulose microcrystalline, lactose monohydrate, crospovidone, povidone, sodium starch glycolate (potato), silica, colloidal hydrated, magnesium stearate
tablet coating - polyvinyl alcohol part-hydrolysed (E1203), macrogol (E1521, polyethylene glycol), talc (E553b), iron oxide red (E172) (40 mg/10 mg only), titanium dioxide (E171) (20 mg/5 mg, 40 mg/5 mg only), iron oxide yellow (E172) (40 mg/5 mg only)

II.2 Drug Substances

The active substances are olmesartan medoxomil and amlodipine besilate. The CEP procedure is used for both active substances. 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 European Pharmacopoeia.

Olmesartan medoxomil
Olmesartan medoxomil is an established active substance, described in the European Pharmacopoeia. The active substance is a white to almost white crystalline powder and is practically insoluble in water and its solubility is pH dependent. Olmesartan medoxomil exhibits polymorphism and one form is consistently used. The active substance is produced by two different manufacturers.

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 from manufacturer one is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. on olmesartan medoxomil and the CEP and contains additional requirements for identification, chromatographic purity, particle size distribution and density. The active substance specification of the MAH is based on the drug substance specifications of both manufacturers and is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for 1 batch by manufacturer one and 3 commercial batches from manufacturer two.

Stability of drug substance
The CEP of manufacturer one does not state a re-test period. The provided stability data support a re-test period of 60 months and does not require any specific storage conditions. According to the manufacturer two, the re-test period of the substance is 2 years 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 European Pharmacopoeia. The active substance is a white or almost white powder. The substance is sparingly soluble in ethanol, slightly soluble in water and 2-propanol and freely soluble in methanol. Amlodipine besilate exhibits polymorphism, the anhydrous from is used for the drug product.

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. on amlodipine and the CEP with additional requirements for related substances, particle size distribution and benzene. The MAH applies tighter acceptance criteria for multiple impurities. The active substance specification of the MAH is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for the drug substance batch used for the manufacture of the biobatches.

Stability of drug substance
The active substance is stable for 18 months 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 development of the routine dissolution method was sufficiently described with regard to the chosen medium and rotation speed, and acceptable limits for dissolution have been set for both active substances.
Bioequivalence studies were carried out for the 40/10 mg and 40/5 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 20/5 mg strength. The 20/5 mg strength is manufactured by the same process as the 40/10 mg strength, the qualitative composition of the two strengths is the same, and the two strengths are dose proportional. Dissolution profiles of the 40/10 mg and 20/5 mg strengths were compared at pH 1.2, pH 4.5, and pH 6.8 using the paddle apparatus operated at 50 rpm. More than 85% of the amlodipine component was dissolved within 15 minutes in all cases. F2 and bootstrap calculations were needed to demonstrate similarity for the olmesartan medoxomil component. The biowaiver is acceptable from a chemical-pharmaceutical point of view.

Manufacturing process
The manufacturing process consists of wet granulation ,fluid bed drying, blending, compression, and coating and has been validated according to relevant European guidelines. Process validation data on the product have been presented for 2 pilot scale batches per strength in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
Except for the iron oxides present in the film-coating, the excipients and other 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 and appearance, identification, dissolution, uniformity of dosage units by content uniformity, assay, impurities and degradation products, water, identification of colour agents, uniformity of mass off subdivided parts and microbiological examination of non-sterile products. The release and shelf life specifications differ with regard to description and appearance and content of specified and total impurities. Identity of the active substances and of the colouring agents as well as content uniformity are only tested at release. The proposed specifications for the drug products are acceptable and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. The provided batch analysis data demonstrate compliance with the release specification in force at the time of analysis

Stability of drug product
Stability data on the product have been provided for 2 pilot scale batches of each strength stored at 25°C/60% RH (24 months), and 40°C/75% RH (6 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. The proposed shelf-life of 24 months without any special storage conditions is acceptable for both packagings.
The provided in-use stability data in the HDPE bottles with desiccant support an in-use shelf life of 100 days when stored at 25°C/60% RH.

Specific measures for 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. Magnesium stearate is of plant and mineral origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Olmesartan medoxomil/Amlodipine ratiopharm 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 Olmesartan medoxomil/Amlodipine ratiopharm 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 a 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 profiles of the test products Olmesartan medoxomil/Amlodipine ratiopharm 40 mg/5 mg and 40 mg/10 mg, film-coated tablets (ratiopharm Nederland B.V.., NL) are compared with the pharmacokinetic profiles of the reference products Sevikar 40 mg/5 mg and 40 mg/10 mg, film-coated tablets (Daiichi Sankyo Netherlands B.V., NL) respectively.

The choice of the reference products in the bioequivalence studies are accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH requested a biowaiver for the 20 mg/5 mg formulation of the fixed-combination of olmesartan medoxomil and amlodipine film-coated tablets based on the bioequivalence study with the 40 mg/10 mg film-coated tablets. The request for biowaiver is fulfilled as follows:

- The pharmaceutical products are manufactured by the same manufacturing process,
- Qualitative composition of the different formulations is the same and appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing.
- The quantitative composition is dose proportional for the 20 mg/5 mg strength.
- Linear pharmacokinetics applied in the therapeutic dose range.

All biowaiver requirements are considered fulfilled. Therefore, a biowaiver can be granted for the 20 mg/5 mg formulation.

Bioequivalence studies

Two single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence studies were carried out under fasted conditions.
Blood samples were collected pre-dose and at 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the studies is acceptable. Food does not affect the bioavailability of olmesartan and amlodipine from the combination of amlodipine and olmesartan. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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.

Bioequivalence Study 1 – olmesartan medoxomil/amlodipine 40 mg/10 mg
Design
The study was carried out in 60 healthy male subjects, aged 19-44 years. Each subject received a single dose (40 mg olmesartan medoxomil and 10 mg amlodipine) of one of the 2 formulations. The tablet was orally administered with 240 ml water after. There were two dosing periods, separated by a washout period of 21 days.

Results
One subject did not return back at the study facility before period 2, one subject was withdrawn due to a low body mass index and 2 subjects were withdrawn due to a positive breath alcohol test before the second period. Therefore, 56 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=56	**AUC_{0-72}** 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_{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 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_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	9868 ± 2956	10028 ± 3021	1416 ± 424	2.17 (1.0 – 4.0)
Reference	9566 ± 2982	9723 ± 3057	1326 ± 420	2.33 (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)	--
$AUC_{0-\infty}$ 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*

Bioequivalence Study 2 – olmesartan medoxomil/amlodipine 40 mg/5 mg
Design
The study was carried out in 44 healthy male subjects, aged 18-44 years. Each subject received a single dose (40 mg olmesartan medoxomil and 5 mg amlodipine of one of the 2 formulations. The tablet was orally administered with 240 ml water after. There were two dosing periods, separated by a washout period of 21 days.

Results

Two subjects dropped-out between periods and one subject reported an adverse event in the first period and was withdrawn from the study. Therefore, 41 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=41	**AUC_{0-72}** 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_{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 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_{0-72} (Amlodipine), AUC_{0-t}, $AUC_{0-\infty}$ (Olmesartan) and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Olmesartan medoxomil/Amlodipine ratiopharm 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.

- 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 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 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Olmesartan medoxomil/Amlodipine ratiopharm 20 mg/5 mg, 40 mg/5 mg and 40 mg/10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Sevikar 20 mg/5 mg, 40 mg/5 mg and 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 ratiopharm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 September 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/3725/1-3/IB/001	Other variation; to implement the outcome of a PSUSA procedure	Y	22-03-2018	Approved	-
NL/H/3725/1-3/IA/002	Replacement or addition of a manufacturer responsible for importation and/or batch release; not including batch control/testing	N	08-05-2018	Approved	-