COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(olmesartan medoxomil/amlodipine besilate)

NL/H/4897/001-003/DC

Date: 19 October 2020

This module reflects the scientific discussion for the approval of Olmesartan medoxomil/Amlodipine Rafarm. The procedure was finalised at 31 August 2020. 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 Rafarm 20 mg/5 mg, 40 mg/5 mg, 40 mg/10 mg, film-coated tablets from Rafarm S.A.

The product is indicated for treatment of essential hypertension.

Olmesartan medoxomil/Amlodipine Rafarm 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 states (CMS) involved in this procedure were Cyprus and Greece.

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 Rafarm is a round film-coated tablet in three strengths:

- 20 mg/5 mg film-coated tablets are white, debossed with “OA1” on one side and plain on the other side.
- 40 mg/5 mg film-coated tablets are white to off-white, debossed with “OA3” on one side and plain on the other side.
- 40 mg/10 mg film-coated tablets are brownish-red, debossed with “OA4” on one side and plain on the other side.

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

The film-coated tablets are packed in OPA/Al/PVC-Al blisters.

The excipients are:

Tablet core
- pregelatinised maize starch
- silicified microcrystalline cellulose (microcrystalline cellulose with silica, colloidal anhydrous)
- lactose monohydrate
- magnesium stearate
- povidone K-30

Film-coating
- polyvinyl alcohol
- titanium dioxide (E171)
- macrogol 3350
- talc
- yellow iron oxide (E172) (40 mg/5 mg, 40 mg/10 mg film-coated tablets only)
- red iron oxide (E172) (40 mg/10 mg film-coated tablets only)

The core tablets of the 40 mg/10 mg and 20 mg/5 mg strengths are dose proportional.

II.2 Drug Substances

The active substances are olmesartan medoxomil and amlodipine besilate, both established active substances described in the European Pharmacopoeia (Ph.Eur.).

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 Ph.Eur.

Olmesartan medoxomil
The active substance is olmesartan medoxomil, an established active substance described in The active substance is a white or almost white crystalline powder and practically insoluble in water, slightly soluble in ethanol (96%) and practically insoluble in heptane. The active substance exhibits polymorphism and the crystalline form is consistently produced.

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. with additional requirement from the CEP. Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance
The active substance is stable for 60 months 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 a white or almost white powder and slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol. The active substance exhibits polymorphism and the crystalline form is produced consistently.

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. with additional requirements from both CEPs. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for five years 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. The excipients are well known and the choices of the packaging and manufacturing process have been justified. Bioequivalence studies were performed with the 40/10 and 40/5 mg drug product. The batches used in the bioequivalence studies have the same composition and are manufactured in the same way as the future commercial batches. The biowaiver of strength for the 20/5 mg strength of the product is acceptable from a chemical-pharmaceutical point of view. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing is a conventional wet granulation process followed by compression, film-

coating and packaging. The manufacturing process was adequately described. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines.

Control of excipients

The quality of excipients used for the manufacture of the film-coated tablets is in compliance with the quality requirements specified in the concerned monographs of the Eur. Ph. except for low substituted silicified microcrystalline cellulose and ferric oxides red and yellow (colorants used in opadrys brown and yellow), which are in compliance with the requirements of the United States Pharmacopeia/National Formulary. 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, identification, dimensions, avg. weight of the tablets, loss on drying, dissolution, uniformity of dosage units , assay, related substances and microbial examination. 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 three 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 three full scale batches of each strength stored at 25°C/60% RH (18 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. No significant changes were seen at both storage conditions. The proposed shelf-life of 24 months without any special storage conditions is justified.

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 Olmesartan medoxomil/Amlodipine Rafarm has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH committed to implement certain limits for two impurities.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Olmesartan medoxomil/Amlodipine Rafarm 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 Rafarm 40 mg/10 mg and 40 mg/5 mg (Rafarm S.A., Greece) 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 54 healthy male subjects, aged 18-44 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 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.
Amlodipine R- and S-isomer blood samples were collected pre-dose and 1, 2, 3, 4, 5, 5.5, 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 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
Four subjects withdrew for personal reasons and one subject was withdrawn on medical grounds. Therefore, 49 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 olmesartan under fasted conditions.

Treatment N=48	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	9310 ± 2656	9421 ± 2694	1358 ± 349	2.375 (1.0 – 4.0)	8.2 ± 1.2
Reference	8416 ± 2340	8521 ± 2380	1233 ± 305	2.25 (1.25 – 4.0)	8.3 ± 0.7
***Ratio (90% CI)**	1.11 (1.04 – 1.18)	--	1.10 (1.03 – 1.18)	--	--
CV (%)	18.2	--	19.4	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

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

Treatment N=47	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	131 ± 34	3.60 ± 0.83	7.0 (3.0-24.0)
Reference	136 ± 36	3.79 ± 0.83	6.5 (5.0 – 14.0)
***Ratio (90% CI)**	0.97 (0.93 – 1.00)	0.95 (0.91 – 0.99)	--
CV (%)	10.4	13.4	

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
CV coefficient of variation

**ln-transformed values*

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

Treatment N=47	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	149 ± 29	3.69 ± 0.67	7.5 (3.0 – 24.0)
Reference	154 ± 30	3.79 ± 0.70	6.5 (5.0 – 14.0)
***Ratio (90% CI)**	0.96 (0.93 – 0.99)	0.97 (0.93 – 1.02)	--
CV (%)	8.9	12.5	

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**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 56 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 21 days.

Olmesartan blood samples were collected pre-dose and 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products. Amlodipine R- and S-isomer blood samples were collected pre-dose and 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 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 and sampling period and scheme are adequate to estimate the pharmacokinetic parameters of interest.

Results

One subject was withdrawn for protocol non-compliance, two subjects were withdrawn on medical grounds and three subjects withdrew for personal reasons. Therefore, 50 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=50	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	8895 ± 2490	8999 ± 2553	1274 ± 352	2.0 (1.0 – 5.0)	8.0 ± 1.3
Reference	8705 ± 2572	8819 ± 2641	1194 ± 358	2.33 (1.0 – 3.67)	8.0 ± 1.3
***Ratio (90% CI)**	1.03 (0.98 – 1.09)	--	1.08 (1.02 – 1.14)	--	--
CV (%)	15.1	--	17.5	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-transformed values*

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine R-isomer under fasted conditions.

Treatment N=48	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	58 ± 16	1.56 ± 0.31	7.75 (4.5 – 12.0)
Reference	59 ± 17	1.63 ± 0.39	7.5 (4.5 – 16.0)
***Ratio (90% CI)**	0.98 (0.95 – 1.01)	0.96 (0.93 – 1.00)	--
CV (%)	8.9	9.5	--

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine S-isomer under fasted conditions.

Treatment N=48	**AUC_{0-72h} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	67 ± 14	1.59 ± 0.31	7.5 (4.5 – 16.0)
Reference	69 ± 15	1.64 ± 0.35	7.75 (4.5 ± 16.0)
***Ratio (90% CI)**	0.99 (0.96 – 1.01)	0.97 (0.94 – 1.00)	--
CV (%)	6.5	9.3	--

AUC_{0-72h} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Olmesartan medoxomil/Amlodipine Rafarm 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 Rafarm.

Table 7. Summary table of safety concerns as approved in RMP

Important identified risks	Foetotoxicity
Important potential risks	None
Missing information	None

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 bioequivalence studies 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 (PL) 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 two 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Olmesartan medoxomil/Amlodipine Rafarm, 20 mg/5 mg, 40 mg/5 mg, 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, 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 Rafarm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 31 August 2020.

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