COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Olmesartan / Amlodipine / HCTZ Win Medica 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/ 5 mg/25 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg, film-coated tablets

(olmesartan medoxomil, amlodipine besilate and hydrochlorothiazide)

NL/H/5221/001-005/DC

Date: 22-11-2021

This module reflects the scientific discussion for the approval of Olmesartan / Amlodipine / HCTZ Win Medica. The procedure was finalised at 30 June 2021. 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 / Amlodipine / HCTZ Win Medica 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/ 5 mg/25 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg, film-coated tablets, from Win Medica S.A.

The product is indicated for the treatment of essential hypertension as an add-on or substitution therapy.

Add-on therapy
Olmesartan / Amlodipine / HCTZ Win Medica is indicated in adult patients whose blood pressure is not adequately controlled on the combination of olmesartan medoxomil and amlodipine taken as dual-component formulation

Substitution therapy
Olmesartan / Amlodipine / HCTZ Win Medica is indicated as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of olmesartan medoxomil, amlodipine and hydrochlorothiazide, taken as a dual-component (olmesartan medoxomil and amlodipine or olmesartan medoxomil and hydrochlorothiazide) and a single-component formulation (hydrochlorothiazide or amlodipine).

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 HCT 20/5/12.5 mg, 40/5/12.5 mg, 40/10/12.5 mg, 40/5/25 mg and 40/10/25 mg film-coated tablets (RVG106667, RVG106671, RVG106672, RVG106637, RVG106674 respectively). The reference products were authorised through procedure NL/H/1858/001-005/DC.

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

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

II. QUALITY ASPECTS

II.1 Introduction

<u>Olmesartan / Amlodipine / HCTZ Win Medica 20 mg/5 mg /12.5 mg</u>
Off white to peach, round, bevel-edged, film-coated tablets debossed with “OC1” on one side and plain on other side.

Olmesartan / Amlodipine / HCTZ Win Medica 40 mg /5 mg/12.5 mg
Light yellow, round, bevel-edged, film-coated tablets debossed with "OC2" on one side and plain on other side.

Olmesartan / Amlodipine / HCTZ Win Medica 40 mg/5 mg/25 mg
Light yellow, oval, bevel-edged, film-coated tablets debossed with "OC3" on one side and plain on other side.

Olmesartan / Amlodipine / HCTZ Win Medica 40 mg/10 mg/12.5 mg
Brick red, round, bevel-edged, film-coated tablets debossed with "OC4" on one side and plain on other side.

Olmesartan / Amlodipine / HCTZ Win Medica 40 mg/10 mg/25 mg
Brick red, oval, bevel-edged, film-coated tablets debossed with "OC5" on one side and plain on other side.

The tablets contain as active substance 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/ 5 mg/25 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg of olmesartan medoxomil, amlodipine (as besilate) and hydrochlorothiazide respectively.

The film-coated tablets are packed in aluminium-aluminium blister packs.

The excipients are:

All strengths

Tablet core – povidone, starch -pregelatinized (maize), silicified cellulose – microcrystalline, lactose monohydrate and magnesium stearate.

20 mg/5 mg/12.5 mg strength

Film-coat - Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172), iron oxide black (E172) and iron oxide red (E172).

40 mg/5 mg/12.5 mg and 40 mg /5 mg/ 25 mg strengths

Film-coat - Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b) and iron oxide yellow (E172).

40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg strengths

Film-coat - Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172) and iron oxide red (E172).

The 20 mg/5 mg/12.5 mg and 40 mg/10 mg/25 mg products are quantitatively proportional (made from the same common blend). The other strengths are not quantitatively proportional to each other.

II.2 Drug Substance

The active substances are olmesartan medoxomil, amlodipine besilate and hydrochlorothiazide, all three established active substances described in the European Pharmacopoeia. Olmesartan medoxomil is a white or almost white, crystalline powder that is practically insoluble in water. Amlodipine besilate is a white or almost white powder, slightly soluble in water. Amlodipine besilate is a racemic compound. Hydrochlorothiazide is a white or almost white, crystalline powder, slightly soluble in water. All three active substances show polymorphism. The manufacturing process followed by the drug substance manufacturers consistently produces the single crystalline form of olmesartan medoxomil (prior art crystalline form), amlodipine besilate (crystalline anhydrous form) and hydrochlorothiazide (form-1), which are stable.

The CEP procedure is used for the 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.

Manufacturing process

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

Quality control of drug substances

Olmesartan medoxomil

The active substance specification is in line with the Ph.Eur. and CEP, with additional requirements for impurities, residual solvents, particle size and microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for eight batches from the proposed production site.

Amlodipine besilate

The active substance specification is in line with the Ph.Eur. and CEP, with additional requirements for residual solvents, besilate ion content, particle size distribution, microbiological quality and content of methyl benzene sulphonate. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches from the proposed production site.

Hydrochlorothiazide
The active substance specification is in line with the Ph.Eur., with additional requirements for residual solvents, particle size distribution and microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two batches from the proposed production site.

Stability of drug substance
Olmesartan medoxomil
The active substance is stable for 60 months when stored in double polyethylene bags (outer black) in a triple laminated bag, placed in a polyethylene container. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Amlodipine besilate
The active substance is stable for five years when stored in a double polyethylene bag (outer black) placed in a polyethylene drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Hydrochlorothiazide
The active substance is stable for 60 months when stored in double polyethylene bags (outer black) placed in either a polyethylene or fibre drum. 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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterization of the reference products, formulation optimization studies, dissolution method development and performance of comparative dissolution studies. The selection of the dissolution method conditions have been justified and the discriminatory power of the method has been demonstrated. Bioequivalence (BE) studies have been performed for four different test product strengths versus their respective originator product strengths. A biowaiver was claimed for the 20 mg/5 mg/12.5 mg product. The drug product batches used in the BE studies were manufactured according to the finalized composition and manufacturing process with an acceptable batch size and are considered representative batches. Comparative dissolution testing at three pHs has been successfully studied in support of bioequivalence and the biowaiver for the 20 mg/5 mg/12.5 mg strength. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The main steps of the manufacturing process are dry mixing, wet granulation, blending and lubrication, compression, coating and packaging. Process validation data on the product has been presented for three pilot scaled batches per strength for the 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg products and for three full scaled batches of the 40 mg/5 mg/25 mg product in accordance with the relevant European guidelines. The products are manufactured using conventional manufacturing techniques. Process validation for full scaled batches of the 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg products will be performed post authorisation.

Control of excipients

The excipients comply with Ph.Eur. or in-house requirements. 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, average weight of tablet, identification, loss on drying, dissolution, uniformity of dosage units, related substances, assay, residual compounds and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Except for loss on drying and related substances, the release and shelf-life requirements are identical.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided on three pilot scaled batches per strength for the 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg products and for three full scaled batches of the 40 mg/5 mg/25 mg product, demonstrating compliance with the release specification.

An adequate risk evaluation for nitrosamine impurities was submitted. All currently identified sources of nitrosamine have been evaluated (EMA/409815/2020). No risk for nitrosamine impurities was identified.

Stability of drug product

Stability data on the product have been provided for three production scaled batches per strength stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product for three years. The batches were stored in Al-Al blisters. At both storage conditions an increase of impurities was seen that was most pronounced at accelerated storage conditions. No clear trends or changes were seen in any of the other tested parameters. All results were in compliance with the shelf-life limits. Photostability studies were performed in accordance with ICH recommendations and showed that the product stable when exposed to light. On basis of the

data submitted, a shelf life was granted of three years without any special storage requirements for the products packed in Al-Al blisters.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate 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 / Amlodipine / HCTZ Win Medica 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 / Amlodipine / HCTZ / Win Medica 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, amlodipine besilate and hydrochlorothiazide 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 four bioequivalence studies, which investigated the bioequivalence between the test and reference olmesartan/ amlodipine/HCTZ formulations. Bioequivalence studies were performed for the following strengths: 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg. A biowaiver was requested for the remaining 20 mg/5 mg/12.5 mg strength.

IV.2 Pharmacokinetics

The MAH conducted four bioequivalence studies in which the pharmacokinetic profile of the test product Olmesartan/amlodipine/HCTZ tablets (Intas Pharmaceuticals Ltd, India) is compared with the pharmacokinetic profile of the reference product Sevikar HCT (Daiichi Sankyo Europe GmbH, the United Kingdom).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver was requested for the remaining 20 mg/5 mg/12.5 mg strength. The 20 mg/5 mg/12.5 mg tablet is dose proportional with the 40 mg/10 mg/25 mg tablets. Dissolution data at three different pH levels showed comparable dissolution between the 40 mg/10 mg/25 mg vs. the 20 mg/5 mg/12.5 mg tablets. Considering the linear pharmacokinetics of the active substances, the biowaiver for the additional strength is acceptable.

Analytical/statistical methods

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

The design of the studies are acceptable.

Bioequivalence studies

Study 1 – 40 mg/10 mg/12.5 mg strength

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 55 healthy male subjects, aged 18-44 years. Each subject received a single dose (40 mg/10 mg/12.5 mg tablet) of the test and reference olmesartan/ amlodipine/HCTZ formulations. The tablets were

orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 24 days.

Blood samples for olmesartan and HCTZ analysis were taken at pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours after administration of the products.

Blood samples for amlodipine analysis were taken at pre-dose and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

Olmesartan medoxomil, amlodipine besilate and hydrochlorothiazide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of Olmesartan medoxomil, amlodipine besilate and hydrochlorothiazide. Therefore, a food interaction study is not deemed necessary. The bioequivalence studies under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Results

Out of a total of 55, 53 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn due to a protocol violation and one subject was withdrawn because of an adverse event (emesis).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan of the test and reference products (40 mg) under fasted conditions.

Treatment N=53	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	10563 ± 2646	10692 ± 2713	1479 ± 335	2.33 (1.0 – 4.5)	8.2 ± 1.5
Reference	10134 ± 2358	10264 ± 2422	1445 ± 371	2.33 (1.0 – 4.5)	8.3 ± 1.7
***Ratio (90% CI)**	1.04 (0.98 – 1.10)	--	1.03 (0.97 – 1.09)	--	--
CV (%)	17.3	--	18.6	--	--

$AUC_{0-\infty}$ 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 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of r-amlodipine of the test and reference products (10 mg) under fasted conditions.

Treatment N=52	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	124 ± 39	3.7 ± 1.1	6.0 (4.0 – 12.0)
Reference	127 ± 37	3.8 ± 1.0	6.5 (4.5 – 12.0)
***Ratio (90% CI)**	0.98 (0.94 – 1.03)	0.97 (0.93 – 1.01)	--
CV (%)	13.3	11.3	--

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 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of s-amlodipine of the test and reference products (10 mg) under fasted conditions.

Treatment N=52	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	232 ± 56	6.2 ± 1.4	6.0 (4.0 – 12.0)
Reference	233 ± 55	6.2 ± 1.5	6.5 (4.5 – 12.0)
***Ratio (90% CI)**	0.99 (0.97 – 1.02)	1.00 (0.97 – 1.04)	--
CV (%)	8.2	11.2	--

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 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of HCTZ of the test and reference products (12.5 mg) under fasted conditions.

Treatment N=53	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	742 ± 210	763 ± 212	104 ± 31	1.67 (0.67 – 4.5)	9.2 ± 1.2
Reference	729 ± 206	750 ± 209	106 ± 33	1.33 (1.0 – 3.33)	9.3 ± 1.2
***Ratio (90% CI)**	1.02 (0.98 – 1.05)	--	0.99 (0.95 – 1.04)	--	--
CV (%)	10.2	--	14.9	--	--

$AUC_{0-\infty}$ 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*

Study 2 – 40 mg/5 mg/25 mg strength

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 55 healthy male subjects, aged 20-44 years. Each subject received a single dose (40 mg/5 mg/25 mg tablet) of the test and reference olmesartan/ amlodipine/HCTZ formulations. The tablets were orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 21 days.

Blood samples for olmesartan and HCTZ analysis were taken at pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours after administration of the products.

Blood samples for amlodipine analysis were taken at pre-dose and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

Results

Out of a total of 55, 48 subjects were eligible for pharmacokinetic analysis. Three subjects were withdrawn on medical grounds in period one. Three other subjects were withdrawn for the same reason in period two. One subject withdrew for personal reasons in period one.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan of the test and reference products (40 mg) 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	10940 ± 2857	11106 ± 2924	1549 ± 395	2.0 (1.0 – 5.0)	8.7 ± 2.0
Reference	10822 ± 2876	10976 ± 2961	1537 ± 331	2.0 (1.0 – 3.5)	8.5 ± 1.5
***Ratio (90% CI)**	1.01 (0.96 – 1.06)	--	1.00 (0.95 – 1.06)	--	--
CV (%)	14.5	--	16.3	--	--

$AUC_{0-\infty}$ 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 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of r-amlodipine of the test and reference products (5 mg) under fasted conditions.

Treatment N=48	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	45 ± 14	1.3 ± 0.3	8.0 (3.0 – 11.0)
Reference	45 ± 15	1.3 ± 0.4	7.5 (3.0 – 14.0)
***Ratio (90% CI)**	1.01 (0.96 – 1.06)	1.00 (0.95 – 1.04)	--
CV (%)	14.5	13.6	--

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 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of s-amlodipine of the test and reference products (5 mg) under fasted conditions.

Treatment N=48	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	110 ± 19	2.7 ± 0.5	8.5 (5.0 – 16.0)
Reference	110 ± 21	2.7 ± 0.5	8.0 (5.0 – 14.0)
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	0.99 (0.96 – 1.02)	--
CV (%)	8.5	8.6	--

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 8. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of HCTZ of the test and reference products (25 mg) 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	1436 ± 339	1470 ± 350	212 ± 52	1.75 (0.75 – 4.0)	9.6 ± 0.9
Reference	1408 ± 328	1442 ± 341	209 ± 65	1.75 (0.75 – 3.5)	9.5 ± 0.9
***Ratio (90% CI)**	1.02 (0.99 – 1.05)	--	1.02 (0.96 – 1.09)	--	--
CV (%)	9.7	--	19.3	--	--

$AUC_{0-\infty}$	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*

Study 3 – 40 mg/10 mg/25 mg strength

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 23-42 years. Each subject received a single dose (40 mg/10 mg/25 mg tablet) of the test and reference olmesartan/ amlodipine/HCTZ formulations. The tablets were orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 22 days.

Blood samples for olmesartan and HCTZ analysis were taken at pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours after administration of the products.

Blood samples for amlodipine analysis were taken at pre-dose and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

Results

Out of a total of 56, 52 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn on medical grounds in period one. Two other subjects were withdrawn for the same reason in period two. One subject withdrew for personal reasons in period two.

Table 9. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan of the test and reference products (40 mg) under fasted conditions.

Treatment N=52	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	13787 ± 3911	13945 ± 3966	2003 ± 553	2.25 (1.0 – 4.5)	8.2 ± 2.0
Reference	13828 ± 4212	13988 ± 4284	2024 ± 538	2.0 (1.25 – 4.0)	8.1 ± 1.8
***Ratio (90% CI)**	1.00 (0.95 – 1.05)	--	0.99 (0.93 – 1.04)	--	--
CV (%)	15.0	--	17.0	--	--

$AUC_{0-\infty}$ 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 10. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of r-amlodipine of the test and reference products (10 mg) under fasted conditions.

Treatment N=52	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	114 ± 35	3.4 ± 0.7	6.0 (4.5 – 12.0)
Reference	118 ± 34	3.5 ± 0.7	6.0 (4.5 – 12.0)
***Ratio (90% CI)**	0.96 (0.93 – 0.99)	0.97 (0.95 – 1.00)	--
CV (%)	8.7	8.7	--

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 11. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of s-amlodipine of the test and reference products (10 mg) under fasted conditions.

Treatment N=48	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	140 ± 28	3.7 ± 0.6	6.25 (4.5 – 12.0)
Reference	143 ± 29	3.7 ± 0.6	6.0 (4.5 – 12.0)
***Ratio (90% CI)**	0.98 (0.96 – 1.00)	1.00 (0.96 – 1.02)	--
CV (%)	5.8	8.4	--

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 12. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of HCTZ of the test and reference products (25 mg) under fasted conditions.

Treatment N=52	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	1412 ± 323	1441 ± 338	206 ± 45	1.63 (0.75 – 4.0)	8.9 ± 0.9
Reference	1357 ± 374	1389 ± 393	207 ± 52	1.5 (0.75 – 3.5)	9.0 ± 1.0
***Ratio (90% CI)**	1.05 (1.01 – 1.09)	--	1.01 (0.95 – 1.06)	--	--
CV (%)	11.9	--	16.8	--	--

$AUC_{0-\infty}$ 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*

Study 4 – 40 mg/5 mg/12.5 mg strength

Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 19-43 years. Each subject received a single dose (40 mg/5 mg/12.5 mg tablet) of the test and reference olmesartan/ amlodipine/HCTZ formulations. The tablets were orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 22 days.

Blood samples for olmesartan and HCTZ analysis were taken at pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hours after administration of the products.

Blood samples for amlodipine analysis were taken at pre-dose and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

Results

Out of a total of 56, 44 subjects were eligible for pharmacokinetic analysis. Two subjects were withdrawn on medical grounds in period one. Four other subjects were withdrawn for the same reason in period two. Two subjects withdrew for personal reasons in period one. Two

other subjects withdrew for the same reason in period two. Two subjects were withdrawn on the grounds of protocol non-compliance in period two.

Table 13. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan of the test and reference products (40 mg) under fasted conditions.

Treatment N=44	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	12306 ± 3212	12449 ± 3281	1852 ± 454	2.0 (1.25 – 4.5)	8.2 ± 2.0
Reference	12649 ± 3216	12809 ± 3342	1901 ± 483	2.25 (1.0 – 4.5)	8.0 ± 1.9
***Ratio (90% CI)**	0.97 (0.91 – 1.04)	--	0.99 (0.90 – 1.06)	--	--
CV (%)	19.6	--	22.2	--	--

$AUC_{0-\infty}$ 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 14. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of r-amlodipine of the test and reference products (5 mg) under fasted conditions.

Treatment N=44	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	51 ± 13	6 ± 0.3	6.0 (4.5 – 12.0)
Reference	52 ± 13	1.5 ± 0.4	6.0 (4.5 – 11.0)
***Ratio (90% CI)**	0.99 (0.95 – 1.03)	1.00 (0.96 – 1.04)	--
CV (%)	11.5	11.0	--

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 15. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of s-amlodipine of the test and reference products (5 mg) under fasted conditions.

Treatment N=44	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	65 ± 13	1.7 ± 0.3	6.0 (4.5 – 12.0)
Reference	65 ± 13	1.7 ± 0.3	6.0 (4.5 – 11.0)
***Ratio (90% CI)**	1.00 (0.96 – 1.00)	1.01 (0.97 – 1.04)	--
CV (%)	7.7	9.2	--

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 16. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of HCTZ of the test and reference products (12.5 mg) under fasted conditions.

Treatment N=52	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	622 ± 142	641 ± 141	93 ± 21	1.5 (0.75 – 4.0)	8.6 ± 1.1
Reference	644 ± 168	665 ± 169	93 ± 27	1.5 (1.0 – 3.5)	8.6 ± 1.1
***Ratio (90% CI)**	0.97 (0.93 – 1.02)	--	1.02 (0.95 – 1.09)	--	--
CV (%)	12.8	--	18.5	--	--

$AUC_{0-\infty}$	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*

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Olmesartan / Amlodipine / HCTZ Win Medica is considered bioequivalent with Sevikar HCT.

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 / Amlodipine / HCTZ Win Medica.

Table 17. Summary table of safety concerns as approved in RMP

Important identified risks	- None
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 HCT. No new clinical studies were conducted. The MAH demonstrated through four 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

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 Sevikar HCT 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/25 mg, film-coated tablets (NL/H/1858/001-005/DC) for key safety messages and with Solifenacin succinate 5/10 mg film-coated tablets (DK/H/2339/001-002/DC) for design and layout. 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 / Amlodipine / HCTZ Win Medica 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/ 5 mg/25 mg, 40 mg/10 mg/12.5 mg and 40 mg/10 mg/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Sevikar HCT. Sevikar HCT 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 concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Olmesartan / Amlodipine / HCTZ Win Medica with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 June 2021.

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