COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Olmesartan medoxomil / Amlodipine / HCT Innovis 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 and 40 mg/10 mg/25 mg, film-coated tablets (olmesartan medoxomil, amlodipine besilate and hydrochlorothiazide)

NL/H/5345/001-005/DC

Date: 29 March 2022

This module reflects the scientific discussion for the approval of Olmesartan medoxomil / Amlodipine / HCT Innovis. The procedure was finalised at 2 November 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 medoxomil / Amlodipine / HCT Innovis 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 and 40 mg/10 mg/25 mg, film-coated tablets , from Innovis Pharma S.A.

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

Add-on therapy
Olmesartan medoxomil / Amlodipine / HCT Innovis 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 medoxomil / Amlodipine / HCT Innovis 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) from Daiichi Sankyo Nederland B.V. The originator product was registered in Europe with 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 medoxomil / Amlodipine / HCT Innovis 20 mg/5 mg /12.5 mg</u>
White, round tablet, with bevelled edges, debossed with “OA” one side and “05” on the other side.

Olmesartan medoxomil / Amlodipine / HCT Innovis 40 mg /5 mg/12.5 mg
Yellow, round tablet, with bevelled edges, debossed with "OA" one side and "06" on the other side.

Olmesartan medoxomil / Amlodipine / HCT Innovis 40 mg/10 mg/12.5 mg
Pink, round tablet, with bevelled edges, debossed with "OA" one side and "03" on the other side.

Olmesartan medoxomil / Amlodipine / HCT Innovis 40 mg/5 mg/25 mg
Yellow, capsule shaped tablet, with bevelled edges, debossed with "OA" one side and "04" on the other side.

Olmesartan medoxomil / Amlodipine / HCT Innovis 40 mg/10 mg/25 mg
Pink, capsule shaped tablet, with bevelled edges, debossed with "OA" one side and "02" on the other side.

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

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

The excipients are:

All strengths

Tablet core – microcrystalline cellulose, lactose monohydrate, povidone (K-30), crospovidone, sodium starch glycolate (type A), sodium colloidal – hydrated and magnesium stearate.

20 mg/5 mg/12.5 mg strength

Film-coat – polyvinyl alcohol – part hydrolysed (E1203), titanium dioxide (E171), macrogol 4000 (E1521) and talc (E553b).

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

Film-coat – polyvinyl alcohol – part hydrolysed (E1203), titanium dioxide (E171), macrogol 4000 (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 – part hydrolysed (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b) and iron oxide red (E172).

The composition of the cores of the 20 mg/5 mg/12.5 mg and 40 mg/10 mg/25 mg tablets is directly proportional. Composition of cores of the further 40 mg strength (40 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg, 40 mg/5 mg/25 mg) compared to 40 mg/10 mg/25 mg tablets differs only in amount of filler (microcrystalline cellulose) due to minor strength of amlodipine besilate and hydrochlorothiazide, respectively.

II.2 Drug Substance

The active substances are olmesartan medoxomil, amlodipine besilate and hydrochlorothiazide, all three established active substances described in the European Pharmacopoeia. According to the Ph.Eur. olmesartan medoxomil is a white or almost white, crystalline powder practically insoluble in water, slightly soluble in ethanol (96%), and practically insoluble in heptane. Amlodipine Besilate is a white or almost white powder slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol (96%), slightly soluble in 2-propanol. Hydrochlorothiazide is a white or almost white, crystalline powder and is very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent). It dissolves in dilute solutions of alkali hydroxides. 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 substance

Olmesartan medoxomil

The active substance specification is in line with the Ph.Eur. and CEP, with additional requirements as stated on the CEP. In addition to these tests the MAH included an additional test for particle size distribution and tests on nitrosamine impurities. 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 six batches from the proposed production sites.

Amlodipine besilate
The active substance specification is in line with the Ph.Eur. and CEP, with additional requirements as stated on the CEP. In addition to these tests the MAH included an additional test for particle size distribution. 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 sites.

Hydrochlorothiazide
The active substance specification is in line with the Ph.Eur. and CEP, with additional requirements as stated on the CEP. Due to drug product requirements the limit for a known impurity is tightened in comparison to Ph.Eur. monograph and additional requirements for particle size distribution are applied. 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 sites.

Stability of drug substance
Olmesartan medoxomil
The active substance is stable for five years when stored in a polyethylene bag in an aluminium bag placed in a fibre drum or a double polyethylene bag (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 polyethylene bag in an aluminium laminated bag with desiccant in between, placed in either a polyethylene container or a cardboard drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Hydrochlorothiazide
The active substance is stable for five years 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 objective of the formulation development studies was to develop an immediate release tablet formulation for Olmesartan/Amlodipine/HCT film-coated tablets which have to be comparable in dissolution behaviour with the originator product resulting in corresponding bioequivalence.

The selection of excipient grade and manufacturer was based on previous formulation experience and knowledge about excipients that have been successfully used in approved products manufactured by wet granulation. All the excipients chosen are commonly used. Drug - excipient compatibility studies were carried out. The excipients meet the Ph. Eur requirements. The concentration of each excipient is within the usual range of application.
The tablet cores are coated with a non-functional coating to provide a distinctive tablet colour to aid in the identification of assorted tablet strengths. The basic coating premixes (yellow, white and pink) are a combination of ingredients established for use in medicinal products. A monograph for the premixes themselves does not appear in any pharmacopoeia; however, the basic coating premix ingredients meet compendial requirements and international standards.

Manufacturing process

The manufacture consist of manufacture of innerphase by wet granulation, manufacture of the left-over active substance dry blend, mixing innerphase with left-over active substance dry blend. Tablets are manufactured by direct compression of the final blend. The tablet cores are film-coated. The manufacturing process has been adequately validated according to European guidelines. 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 and 40 mg/5 mg/12.5 mg products and two pilot scaled batches per strength for the remaining strengths in accordance with the relevant European guidelines. Furthermore general process validation data for three batches of 40/5/25 mg tablets and for three batches of 40/5/12.5 mg tablets and process validation reports for two batches of 20/5/12.5 mg, 40/10/12.5 mg and 40/10/25 mg strength manufactured at another manufacturing site are presented.

Control of excipients

The excipients comply with Ph.Eur. 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 appearance, identification, dissolution, uniformity of dosage units by content uniformity, assay, impurities, water and microbiological purity. 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 has been presented for three batches per strength for the 20 mg/5 mg/12.5 mg and 40 mg/5 mg/12.5 mg products and two batches per strength for the remaining strengths from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches per strength for the 20 mg/5 mg/12.5 mg and 40 mg/5 mg/12.5 mg products and two batches per strength for the remaining strengths for one manufacturing site. Furthermore, stability data has been submitted for two batches per strength for the other manufacturing site in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Long-term stability data (25°C/60% RH) covering 18-24 months) and accelerated stability data (40°C/75% RH) covering 6 months are provided for both manufacturing sites. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-OPA/Al/PVC blister. Photostability study showed that the product is not sensitive to light when stored in the original package. The product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: "Store container in the original package".

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 / HCT Innovis 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 / HCT Innovis 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 three bioequivalence studies, which investigated the bioequivalence between the test and reference Olmesartan medoxomil/ amlodipine/HCT formulations. Bioequivalence studies were performed for the following strengths: 40 mg/5 mg/12.5 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 and 40 mg/5 mg/25 mg strengths.

IV.2 Pharmacokinetics

The MAH conducted four bioequivalence studies in which the pharmacokinetic profile of the test product Olmesartan medoxomil / Amlodipine/HCT Innovis (Teva Pharmaceuticals, India) is compared with the pharmacokinetic profile of the reference product Sevikar HCT (Daiichi Sankyo, Germany).

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

Biowaiver

The MAH proposes to waive additional BE-studies of olmesartan medoxomil, amlodipine and hydrochlorothiazide tablets for the 20 mg/5 mg/12.5 mg and the 40 mg/5 mg/25 mg strength. The dissolution profiles of Olmesartan medoxomil/ Amlodipine/ HCT 40 mg/10 mg/25 mg and 40 mg /5 mg/12.5 mg biobatches tested against the Olmesartan medoxomil/ Amlodipine/Hydrochlorothiazide 40 mg/5 mg/25 mg and 20 mg/5 mg/12.5 mg tablets are considered similar in all pH values tested and in QC medium. Based upon dose proportionality with the 40 mg/10 mg/25 mg strength and supportive dissolution data, the biowaiver for the 20 mg/5 mg/12.5 mg tablet is acceptable. Based upon the bracketing approach of the formulation sued in the bioequivalence studies and supportive dissolution data, the biowaiver for the 40 mg/5 mg/25 mg strength is acceptable.

This product 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 study under fasting conditions is in accordance with

CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

The design of the studies 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.

Bioequivalence studies

Study 1: 40 mg/10 mg/25 mg strength
Design
An open label, randomized, single dose, two way crossover, bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 19-41 years. Each subject received a single dose (40 mg/10 mg/25 mg; 1 x 40 mg/10 mg/25 mg tablet) of both the test and the reference olmesartan medoxomil/amlodipine besilate/hydrochlorothiazide formulations. The tablet was 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 were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 5, 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.

Results
Out of a total of 54, 44 subjects were eligible for pharmacokinetic analysis. Four subjects were withdrawn because of adverse events, two subjects did not check in period two, two other subjects were withdrawn due to a positive alcohol test and one subject had missing samples. As per protocol the first 30 subjects who completed the study were analysed for amlodipine and hydrochlorothiazide

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Olmesartan (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	10730 ± 2619	10882 ± 2647	1460 ± 364	2.33 (1.33– 4.0)	8.0 ± 1.4
Reference	11253 ± 3038	11411 ± 3084	1581 ± 353	2.0 (1.33 – 4.0)	7.9 ± 1.4
***Ratio (90% CI)**	0.96 (0.91 – 1.01)	--	0.91 (0.87 – 0.93)	--	--
CV (%)	13.4	--	14.7	--	--

$AUC_{0-\infty}$	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 amlodipine (10 mg) under fasted conditions.

Treatment N=30	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	365 ± 56	9.1 ± 1.4	6.5 (5.0– 12.0)
Reference	351 ± 59	8.9 ± 1.5	6.75 (5.0 – 14.0)
***Ratio (90% CI)**	1.04 (1.01 – 1.08)	1.04 (0.99 – 1.08)	--
CV (%)	7.9	10	--

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
CV	coefficient of variation

**ln-transformed values*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Hydrochlorothiazide (25 mg) under fasted conditions.

Treatment N=29	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	1710 ± 285	1764 ± 297	237 ± 53	1.67 (1.0– 4.0)	10.5 ± 1.0
Reference	1683 ± 326	1734 ± 338	235 ± 59	2.0 (0.73 – 3.5)	10.3 ± 1.0
***Ratio (90% CI)**	1.02 (0.97 – 1.07)	--	1.01 (0.94 – 1.10)	--	--
CV (%)	10.5	--	17.6	--	--

$AUC_{0-\infty}$	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

**In-transformed values*

Study 2: 40 mg/10 mg/12.5 mg strength

Design

An open label, randomized, single dose, two way crossover, bioequivalence study was carried out under fasted conditions in 72 healthy male subjects, aged 18-43 years. Each subject received a single dose (40 mg/10 mg/12.5 mg; 1 x 40 mg/10 mg/12.5 mg tablet) of both the test and the reference olmesartan medoxomil/amlodipine besilate/hydrochlorothiazide formulations. The tablet was 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 were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 5, 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.

Results

Out of a total of 72, 68 subjects were eligible for pharmacokinetic analysis. Two subjects were withdrawn because of adverse events, one subject did not check in period two and one subject withdrew due to personal reasons. As per protocol the first 30 subjects who completed the study were analysed for amlodipine and hydrochlorothiazide

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Olmesartan (40 mg) under fasted conditions.

Treatment N=68	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	12063 ± 2933	12234 ± 2978	1672 ± 439	2.33 (1.00– 6.0)	8.6 ± 1.2
Reference	12291 ± 2596	12456 ± 2637	1777 ± 343	2.33 (1.33 – 4.0)	8.6 ± 1.2
***Ratio (90% CI)**	0.97 (0.93 – 1.01)	--	0.92 (0.88 – 0.97)	--	--
CV (%)	13.3	--	16.6	--	--

$AUC_{0-\infty}$ 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

**In-transformed values*

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Amlodipine (10 mg) under fasted conditions.

Treatment N=30	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)

Test	376 ± 65	9.3 ± 1.6	6.5 (5.0 – 14.0)
Reference	369 ± 70	9.2 ± 1.4	6.75 (5.0 – 11.0)
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	1.01 (0.97 – 1.05)	--
CV (%)	9	9.3	--

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
CV coefficient of variation

**In-transformed values*

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Hydrochlorothiazide (12.5 mg) under fasted conditions.

Treatment N=30	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	836 ± 134	861 ± 139	113 ± 25	2.17 (1.0– 4.0)	10.0 ± 1.3
Reference	831 ± 159	858 ± 162	115 ± 21	1.84 (0.73 – 3.0)	10.0 ± 1.0
***Ratio (90% CI)**	1.01 (0.98 – 1.05)	--	0.98 (0.94 – 1.02)	--	--
CV (%)	7.6	--	9.1	--	--

$AUC_{0-\infty}$ 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

**In-transformed values*

Study 3: 40 mg/5 mg/12.5 mg strength

Design

An open label, randomized, single dose, two way crossover, bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 19-45 years. Each subject received a single dose (40 mg/5 mg/12.5 mg; 1 x 40 mg/5 mg/12.5 mg tablet) of both the test and the reference olmesartan medoxomil/amlodipine besilate/hydrochlorothiazide formulations. The tablet was 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 were collected at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 5, 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.

Results

Out of a total of 54, 42 subjects were eligible for pharmacokinetic analysis. Eight subjects were withdrawn because of adverse events, four subject did not check in period two and one subject withdrew due to alcohol abuse. As per protocol the first 30 subjects who completed the study were analysed for amlodipine and hydrochlorothiazide

Table 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Olmesartan (40 mg) under fasted conditions.

Treatment N=68	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	12675 ± 3194	12859 ± 3278	1693 ± 329	2.0 (1.33 – 4.0)	8.4 ± 1.1
Reference	12622 ± 2913	12804 ± 2972	1745 ± 385	2.33 (1.33 – 4.0)	8.4 ± 1.4
***Ratio (90% CI)**	0.99 (0.95 – 1.04)	--	0.98 (0.93 – 1.03)	--	--
CV (%)	13	--	13.1	--	--

$AUC_{0-\infty}$ 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 8. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Amlodipine (5 mg) under fasted conditions.

Treatment N=30	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	175 ± 32	4.5 ± 0.6	6.5 (5.0 – 12.0)
Reference	178 ± 36	4.5 ± 0.8	6.75 (5.0 – 11.0)
***Ratio (90% CI)**	1.00 (0.96 – 1.03)	1.00 (0.96 – 1.05)	--
CV (%)	7.8	9.9	--

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
CV	coefficient of variation

**ln-transformed values*

Table 9. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of Hydrochlorothiazide (12.5 mg) under fasted conditions.

Treatment N=29	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 ± 160	769 ± 162	100 ± 22	1.73 (1.0– 4.0)	10.1 ± 1.1
Reference	732 ± 147	760 ± 147	106 ± 23	1.67 (1.0 – 4.0)	10.0 ± 1.2
***Ratio (90% CI)**	1.01 (0.98 – 1.05)	--	0.95 (0.90 – 0.99)	--	--
CV (%)	7.2	--	11.2	--	--

$AUC_{0-\infty}$	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*

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 / HCT Innovis 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 / HCT Innovis.

Table 10. 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. No new clinical studies were conducted. The MAH demonstrated through three 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 language used for the purpose of user testing the PL was English. 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 / HCT Innovis 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 and 40 mg/10 mg/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Sevikar. 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 concerned member state, on the basis of the data submitted,

considered that essential similarity has been demonstrated for Olmesartan medoxomil / Amlodipine / HCT Innovis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 November 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