COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Olmesartan medoxomil/Amlodipine/HCT Accord 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, hydrochlorothiazide)

NL/H/6466/001-005/DC

Date: 7 August 2025

This module reflects the scientific discussion for the approval of Olmesartan medoxomil/Amlodipine/HCT Accord 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. The procedure was finalised at 9 March 2020 in Spain (ES/H/0623/001-005/DC). After a transfer on 18 June 2025, the current RMS is the Netherlands. For information on changes after the finalisation 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Accord 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, from Accord Healthcare B.V.

The product is indicated in the treatment of essential hypertension.
Add-on therapy
Olmesartan medoxomil/Amlodipine/HCT Accord film-coated tablets 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 Accord film-coated tablets 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 current SmPC.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as film-coated tablets, the description of the different strengths are indicated below:

Olmesartan medoxomil/Amlodipine/HCT Accord film-coated tablets 20 mg/5 mg/12.5 mg
Off white to peach, round, bevel-edged, film-coated tablets debossed with "OC1" on one side and plain on other side.

Olmesartan medoxomil/Amlodipine/HCT Accord film-coated tablets 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 medoxomil/Amlodipine/HCT Accord film-coated tablets 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 medoxomil/Amlodipine/HCT Accord film-coated tablets 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 medoxomil/Amlodipine/HCT Accord film-coated tablets 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 maximum daily dose 40 mg/10 mg/ 25 mg (Olmesartan/ Amlodipine/Hydrochlorothiazide) Olmesartan medoxomil/Amlodipine/HCT Accord tablets are packed in Alu-Alu blisters.

All the components of the product are included in the composition table. Excipients are listed specifying their common name, the quantity present, their function and a reference to a relevant standard.

Olmesartan medoxomil/Amlodipine/HCT Accord tablets are packed in Alu-Alu blisters and/or PPCP (Polypropylen Co-Polymer) containers.

II.2 Drug Substance

Olmesartan medoxomil
The quality of the active ingredient Olmesartan medoxomil is supported by CEP. Copies of the most current CEPs are included in the dossier.

Amlodipine Besilate
The quality of the active ingredient Amlodipine Besilat is supported by CEP. Copies of the most current CEPs are included in the dossier.

Hydrochlorothiazide
The quality of the active ingredient Hydrochlorothiazide is supported by CEP. Copies of the most current CEPs are included in the dossier.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

Manufacturing process
The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are provided.

Control of excipients
Excipients used are well known and of appropriate quality.

Quality control of drug product
The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

The finished product is packed packed in Alu-Alu blisters and/or PPCP containers (bulk storage/ transportation pack), The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability of drug product

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 3 years.
Storage conditions: This medicinal product does not require any special storage conditions.

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

None of the excipients is of animal origin, except lactose monohydrate. Lactose monohydrate of animal origin is used in the formulation. It is confirmed by the manufacturer that the Lactose monohydrate is prepared without the use of other ruminant material than milk and calf rennet. Milk is sourced from healthy animals in the same conditions as milk collected for human consumption in accordance with the EU food hygiene regulations.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Olmesartan medomixil/Amlodipine/HCT Accord 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 is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of olmesartan, amlodipine and hydrochlorothiazide are well known. As olmesartan, amlodipine and hydrochlorothiazide are widely used, well-known actives substances, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Olmesartan/amlodipine/hydrochlorothiazide is a well-known combination of substances with established efficacy and safety. A clinical overview has been provided, which is based on

scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted four bioequivalence studies concerning the following strengths: 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, according to the *Guideline on the investigation of bioequivalence*, which are discussed below.

IV.2 Pharmacokinetics

Biowaiver

This application concerns five strengths, i.e., 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, and the bioequivalence studies have been carried out with the 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 strengths.

The criteria according to the *Guideline on the Investigation of Bioequivalence* for waiving the 20/5/12.5 mg strength are fulfilled as:

- The five strengths are manufactured with the same process.
- The qualitative composition of all the strengths is the same.
- The composition of the strengths is quantitatively proportional.
- Appropriate dissolution profiles between the different strengths have confirmed to be similar.

Bioequivalence studies

Study code 785-15

GCP compliance

The studies were conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities

Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-38248 1, Gujarat, India.

Design

A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 55 healthy male subjects, aged 22– 38 years. Each subject received a single dose (40/10/12.5 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after

an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 24 days.

Analytical and statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.

The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.

The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

55 subjects were included in the study. 55 subjects were treated; 53 subjects completed the study and 53 were used in the statistical analysis according to the protocol. The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Descriptive statistics

Olmesartan

Descriptive Statistics of Formulation Means for Olmesartan (N = 53)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	2.333 (1.000 - 4.500)	2.333 (1.000 - 4.500)
C_{max} (ng/mL)	1478.728 ± 334.7095	1444.866 ± 370.5367
AUC_{0-t} (ng.h/mL)	10562.816 ± 2645.6600	10134.393 ± 2358.4022
$AUC_{0-\infty}$ (ng.h/mL)	10692.316 ± 2712.7588	10263.782 ± 2421.7541
λ_z (1/h)	0.087 ± 0.0138	0.087 ± 0.0155
$t_{½}$ (h)	8.196 ± 1.4864	8.275 ± 1.6692
AUC_%Extrap_obs (%)	1.146 ± 0.7953	1.191 ± 0.8587

*T_{max} is represented in median (min-max) value.

Hydrochlorothiazide

Descriptive Statistics of Formulation Means for Hydrochlorothiazide (N = 53)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	1.667 (0.667 - 4.500)	1.333 (1.000 - 3.333)
C_{max} (ng/mL)	104.023 ± 31.1390	105.644 ± 33.1844
AUC_{0-t} (ng.h/mL)	742.070 ± 209.9743	728.726 ± 206.3590
$AUC_{0-\infty}$ (ng.h/mL)	763.308 ± 212.2156	750.394 ± 209.1588
λ_z (1/h)	0.077 ± 0.0136	0.076 ± 0.0101
$t_{½}$ (h)	9.175 ± 1.1937	9.327 ± 1.1800
AUC_%Extrap_obs (%)	2.940 ± 0.9580	3.036 ± 0.9610

*T_{max} is represented in median (min-max) value.

S-Amlodipine

_Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T^	Reference Product-R
T_{max} (h)*	6.009 (4.000 - 12.000)	6.500 (4.500 - 12.000)
C_{max} (ng/mL)	6.183 ± 1.4458	6.162 ± 1.4827
AUC_{0-72} (ng.h/mL)	232.400 ± 55.7763	233.214 ± 55.3779

*T_{max} is represented in median (min-max) value. ^N = 52.

R-Amlodipine

_Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T^	Reference Product-R
T_{max} (h)*	6.000 (4.000 - 12.000)	6.500 (4.500 - 12.000)
C_{max} (ng/mL)	3.739 ± 1.0523	3.777 ± 1.0336
AUC_{0-72} (ng.h/mL)	123.750 ± 39.0109	126.715 ± 36.6803

*T_{max} is represented in median (min-max) value. ^N = 52.

Bioequivalence evaluation

Olmesartan

Relative Bioavailability Results for Olmesartan (N = 53)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	1437.172	1400.764	102.6	96.63 - 108.94	18.6	100.0
$lnAUC_{0-t}$	10240.513	9876.228	103.7	98.05 - 109.65	17.3	100.0
$lnAUC_{0-\infty}$	10360.067	9995.845	103.6	98.05 - 109.55	17.2	100.0

(Refer Table No. 14.2.1.1)

Hydrochlorothiazide

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	99.556	100.327	99.2	94.57 - 104.12	14.9	100.0
$lnAUC_{0-t}$	713.131	700.219	101.8	98.53 - 105.27	10.2	100.0
$lnAUC_{0-\infty}$	734.763	722.184	101.7	98.45 - 105.14	10.1	100.0

(Refer Table No. 14.2.4.1)

S-Amlodipine

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T^	Reference Product-R	Ratio (T/R)%			
lnC_{max}	6.021	6.015	100.1	96.55 - 103.80	11.1	100.0
$lnAUC_{0-72}$	226.143	227.807	99.3	96.65 - 101.96	8.2	100.0

^N = 52.

R-Amlodipine

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T^	Reference Product-R	Ratio (T/R)%			
lnC_{max}	3.594	3.660	98.2	94.03 - 102.56	13.3	100.0
$lnAUC_{0-72}$	118.487	122.254	96.9	93.41 - 100.56	11.3	100.0

^N = 52.

Based on the submitted bioequivalence study, Olmesartan medoxomil/Amlodipine/HCT Accord 40 mg/10 mg/12.5 mg film-coated tablets, when compared with the Reference Product Sevikar HCT® 40 mg/10 mg/12.5 mg film-coated tablets in fasting condition seems to meet the bioequivalence criteria with respect to the Cmax and AUC.

Study code 0965-18

GCP compliance
The studies were conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities
Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-38248 1, Gujarat, India.

Design.
A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 25 – 36 years. Each subject received a single dose (40/10/25 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 22 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
56 subjects were dosed and 52 subjects completed the study and used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Descriptive statistics

Olmesartan

Descriptive Statistics of Formulation Means for Olmesartan (N = 52)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	2.250 (1.000 - 4.517)	2.000 (1.250 - 4.000)
C_{max} (ng/mL)	2003.232 ± 553.4829	2023.892 ± 538.1066
AUC_{0-t} (ng.h/mL)	13786.627 ± 3910.8206	13827.703 ± 4211.9324
$AUC_{0-\infty}$ (ng.h/mL)	13945.386 ± 3965.5287	13987.707 ± 4283.5114
λ_z (1/h)	0.087 ± 0.0150	0.088 ± 0.0149
$t_{½}$ (h)	8.231 ± 2.0232	8.135 ± 1.8368
AUC_%Extrap_obs (%)	1.113 ± 0.9101	1.083 ± 0.9066

*T_{max} is represented as median (min-max) value.

Hydrochlorothiazide

Descriptive Statistics of Formulation Means for Hydrochlorothiazide (N = 52)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	1.634 (0.750 - 4.000)	1.500 (0.750 - 4.000)
C_{max} (ng/mL)	206.128 ± 44.5555	206.714 ± 52.3177
AUC_{0-t} (ng.h/mL)	1412.161 ± 322.5181	1357.402 ± 373.8705
$AUC_{0-\infty}$ (ng.h/mL)	1440.897 ± 337.5881	1388.601 ± 392.5894
λ_z (1/h)	0.079 ± 0.0077	0.078 ± 0.0082
$t_{½}$ (h)	8.891 ± 0.9205	9.020 ± 1.0447
AUC_%Extrap_obs (%)	1.900 ± 0.7522	2.133 ± 0.9224

*T_{max} is represented as median (min-max) value.

S-Amlodipine

Descriptive Statistics of Formulation Means for S-amlodipine (N = 52)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	6.250 (4.500 - 12.000)	6.009 (4.500 - 12.017)
C_{max} (ng/mL)	3.651 ± 0.6201	3.673 ± 0.6230
AUC_{0-72} (ng.h/mL)	139.772 ± 27.9213	142.801 ± 28.9166

*T_{max} is represented as median (min-max) value.

R-Amlodipine

Descriptive Statistics of Formulation Means for R-amlodipine (N = 52)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	6.000 (4.500 - 12.017)	6.000 (4.500 - 12.017)
C_{max} (ng/mL)	3.380 ± 0.7311	3.465 ± 0.7075
AUC_{0-72} (ng.h/mL)	113.969 ± 35.2221	117.905 ± 34.0098

*T_{max} is represented as median (min-max) value.

Bioequivalence evaluation

Olmesartan

Relative Bioavailability Results for Olmesartan (N = 52)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	1923.938	1952.238	98.6	93.23 - 104.18	17.0	100.0
$lnAUC_{0-t}$	13203.751	13184.677	100.1	95.34 - 105.19	15.0	100.0
$lnAUC_{0-\infty}$	13353.748	13329.772	100.2	95.33 - 105.28	15.2	100.0

Hydrochlorothiazide

Relative Bioavailability Results for Hydrochlorothiazide (N = 52)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	201.738	200.522	100.6	95.24 - 106.27	16.8	100.0
$lnAUC_{0-t}$	1376.610	1311.439	105.0	100.95 - 109.15	11.9	100.0
$lnAUC_{0-\infty}$	1403.354	1340.125	104.7	100.74 - 108.85	11.8	100.0

S-Amlodipine

Relative Bioavailability Results for S-amlodipine (N = 52)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	3.604	3.622	99.5	96.82 - 102.31	8.4	100.0
$lnAUC_{0-72}$	137.191	139.679	98.2	96.35 - 100.12	5.8	100.0

R-Amlodipine

Relative Bioavailability Results for R-amlodipine (N = 52)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	3.306	3.395	97.4	94.63 - 100.21	8.7	100.0
$lnAUC_{0-72}$	108.389	112.767	96.1	93.41 - 98.90	8.7	100.0

Based on the submitted bioequivalence study, Olmesartan medoxomil/Amlodipine/HCT Accord 40 mg/10 mg/25 mg film-coated tablets, when compared with the Reference Product Sevikar HCT® 40 mg/10 mg/25 mg film-coated tablets in fasting condition seems to meet the bioequivalence criteria with respect to the Cmax and AUC.

Study code 0966-18

GCP compliance
The studies were conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities
Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-38248 1, Gujarat, India.

Design.
A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 25 – 36 years. Each subject received a single dose (40/5/12.5 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 22 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
56 subjects were dosed and 44 subjects completed the study and used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Descriptive statistics

Olmesartan

Descriptive Statistics of Formulation Means for Olmesartan (N = 44)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	2.000 (1.250 - 4.500)	2.250 (1.017 - 4.500)
C_{max} (ng/mL)	1852.499 ± 453.6721	1901.095 ± 483.0652
AUC_{0-t} (ng.h/mL)	12306.110 ± 3212.3058	12648.887 ± 3215.7913
$AUC_{0-\infty}$ (ng.h/mL)	12449.048 ± 3281.1301	12808.583 ± 3341.6847
λ_z (1/h)	0.088 ± 0.0150	0.089 ± 0.0146
$t_{½}$ (h)	8.193 ± 1.9796	8.084 ± 1.8899
AUC_%Extrap_obs (%)	1.099 ± 1.1133	1.113 ± 1.2349

*T_{max} is represented as median (min-max) value.

Hydrochlorothiazide

Descriptive Statistics of Formulation Means for Hydrochlorothiazide (N = 44)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	1.500 (0.750 - 4.000)	1.500 (1.000 - 3.500)
C_{max} (ng/mL)	93.422 ± 20.6261	93.324 ± 27.0705
AUC_{0-t} (ng.h/mL)	621.541 ± 142.0455	644.283 ± 168.4212
$AUC_{0-\infty}$ (ng.h/mL)	641.360 ± 141.1780	665.331 ± 169.0912
λ_z (1/h)	0.082 ± 0.0114	0.082 ± 0.0118
$t_{½}$ (h)	8.598 ± 1.1001	8.574 ± 1.1107
AUC_%Extrap_obs (%)	3.268 ± 1.1651	3.324 ± 1.2918

*T_{max} is represented as median (min-max) value.

S-Amlodipine

Descriptive Statistics of Formulation Means for S-amlodipine (N = 44)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	6.000 (4.500 - 12.000)	6.000 (4.500 - 11.000)
C_{max} (ng/mL)	1.719 ± 0.2677	1.716 ± 0.3471
AUC_{0-72} (ng.h/mL)	64.735 ± 13.2173	65.068 ± 13.1449

*T_{max} is represented as median (min-max) value.

R-Amlodipine

Descriptive Statistics of Formulation Means for R-amlodipine (N = 44)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	6.009 (4.500 - 12.000)	6.000 (4.500 - 11.033)
C_{max} (ng/mL)	1.556 ± 0.2622	1.572 ± 0.3586
AUC_{0-72} (ng.h/mL)	51.439 ± 12.5711	52.045 ± 13.3472

*T_{max} is represented as median (min-max) value.

Bioequivalence evaluation

Olmesartan

Relative Bioavailability Results for Olmesartan (N = 44)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
$\ln C_{max}$	1796.953	1842.435	97.5	90.16 - 105.50	22.2	99.8
$\ln AUC_{0-t}$	11913.563	12271.962	97.1	90.54 - 104.09	19.6	100.0
$\ln AUC_{0-\infty}$	12046.747	12411.027	97.1	90.56 - 104.03	19.5	100.0

Hydrocholothiazide

Relative Bioavailability Results for Hydrochlorothiazide (N = 44)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	91.255	89.750	101.7	95.20 - 108.59	18.5	100.0
$lnAUC_{0-t}$	606.084	623.479	97.2	92.85 - 101.77	12.8	100.0
$lnAUC_{0-\infty}$	626.607	644.971	97.2	92.96 - 101.53	12.3	100.0

S-Amlodipine

Relative Bioavailability Results for S-amlodipine (N = 44)

_Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	1.699	1.682	101.0	97.71 - 104.32	9.2	100.0
$lnAUC_{0-72}$	63.497	63.841	99.5	96.77 - 102.23	7.7	100.0

R-Amlodipine

Relative Bioavailability Results for R-amlodipine (N = 44)

_Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	1.535	1.534	100.1	96.25 - 104.10	11.0	100.0
$lnAUC_{0-72}$	50.048	50.393	99.3	95.33 - 103.46	11.5	100.0

Based on the submitted bioequivalence study, Olmesartan medoxomil/Amlodipine/HCT Accord 40 mg/5 mg/12.5 mg film-coated tablets, when compared with the Reference Product Sevikar HCT® 40 mg/5 mg/12.5 mg film-coated tablets in fasting condition seems to meet the bioequivalence criteria with respect to the Cmax and AUC.

Study code 1035-16

GCP compliance

The studies were conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities

Lambda Therapeutic Research Ltd. Lambda House, Plot No. 38, Survey No. 388, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-38248 1, Gujarat, India.

Design

A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 55 healthy male subjects, aged 25 – 42 years. Each subject received a single dose (40/5/25 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 21 days.

Analytical and statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.

The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.

The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

55 subjects were included in the study into two groups. 55 subjects were treated; 48 subjects completed the study and used in the statistical analysis according to the protocol.

No group*formulation interaction was observed.

The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Descriptive statistics

Olmesartan

Descriptive Statistics of Formulation Means for Olmesartan (N = 48)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	2.009 (1.000 - 5.000)	2.009 (1.017 - 3.500)
C_{max} (ng/mL)	1548.645 ± 395.2122	1536.664 ± 330.9200
AUC_{0-t} (ng.h/mL)	10940.056 ± 2857.2738	10822.498 ± 2876.0900
$AUC_{0-\infty}$ (ng.h/mL)	11105.794 ± 2923.8848	10976.080 ± 2961.1388
λ_z (1/h)	0.083 ± 0.0173	0.084 ± 0.0134
$t_{½}$ (h)	8.737 ± 2.0365	8.481 ± 1.5183
AUC_%Extrap_obs (%)	1.429 ± 1.0169	1.293 ± 0.7899

*T_{max} is represented in median (min-max) value.

Hydrochlorothiazide

Descriptive Statistics of Formulation Means for Hydrochlorothiazide (N = 48)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	1.759 (0.750 - 4.000)	1.750 (0.750 - 3.500)
C_{max} (ng/mL)	211.798 ± 51.8177	209.497 ± 64.8298
AUC_{0-t} (ng.h/mL)	1435.734 ± 338.8126	1407.918 ± 328.4534
$AUC_{0-\infty}$ (ng.h/mL)	1470.075 ± 350.0507	1441.741 ± 340.5641
λ_z (1/h)	0.073 ± 0.0068	0.074 ± 0.0073
$t_{½}$ (h)	9.586 ± 0.8854	9.494 ± 0.9106
AUC_%Extrap_obs (%)	2.293 ± 0.7229	2.297 ± 0.7522

*T_{max} is represented in median (min-max) value.

S-Amlodipine

Descriptive Statistics of Formulation Means for S-amlodipine (N = 48)

_Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	8.509 (5.000 - 16.000)	8.009 (5.000 - 14.000)
C_{max} (ng/mL)	2.695 ± 0.4560	2.736 ± 0.5051
AUC_{0-72} (ng.h/mL)	109.679 ± 19.1000	110.497 ± 21.4339

*T_{max} is represented in median (min-max) value.

R-Amlodipine

Descriptive Statistics of Formulation Means for R-amlodipine (N = 48)

Parameters (Units)	Mean ± SD (untransformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)*	8.000 (3.000 - 11.000)	7.500 (3.000 - 14.017)
C_{max} (ng/mL)	1.318 ± 0.3252	1.327 ± 0.3628
AUC_{0-72} (ng.h/mL)	45.070 ± 14.4227	44.597 ± 15.4840

*T_{max} is represented in median (min-max) value.

Bioequivalence evaluation

Olmesartan

Relative Bioavailability Results for Olmesartan (N = 48)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	1509.172	1509.555	100.0	94.58 - 105.67	16.3	100.0
$lnAUC_{0-t}$	10604.269	10518.922	100.8	95.95 - 105.92	14.5	100.0
$lnAUC_{0-\infty}$	10762.027	10659.478	101.0	96.09 - 106.09	14.5	100.0

Hydrochlorothiazide

Relative Bioavailability Results for Hydrochlorothiazide (N = 48)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	202.588	198.289	102.2	95.69 - 109.09	19.3	100.0
$lnAUC_{0-t}$	1412.555	1386.462	101.9	98.56 - 105.32	9.7	100.0
$lnAUC_{0-\infty}$	1446.193	1419.438	101.9	98.60 - 105.28	9.6	100.0

S-Amlodipine

Relative Bioavailability Results for S-amlodipine (N = 48)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	2.665	2.692	99.0	96.13 - 101.96	8.6	100.0
$lnAUC_{0-72}$	108.425	108.641	99.8	96.95 - 102.73	8.5	100.0

R-Amlodipine

Relative Bioavailability Results for R-amlodipine (N = 48)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R) %			
lnC_{max}	1.279	1.284	99.6	95.11 - 104.37	13.6	100.0
$lnAUC_{0-72}$	42.843	42.450	100.9	96.05 - 106.05	14.5	100.0

Based on the submitted bioequivalence study, Olmesartan medoxomil/Amlodipine/HCT Accord 40 mg/5 mg/25 mg film-coated tablets, when compared with the Reference Product Sevikar HCT® 40 mg/5 mg/25 mg film-coated tablets in fasting condition seems to meet the bioequivalence criteria with respect to the Cmax and AUC.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Olmesartan medoxomil/Amlodipine/HCT Accord is considered bioequivalent with Sevikar.

The results of studies 785-15, 0965-18, 0966-18 and 1035-16 with the 40/10/12.5 mg, 40/10/25, 40/5/12.5 mg and 40/5/25 mg formulation respectively can be extrapolated to the other strength 20/5/12.5 mg, according to conditions in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Olmesartan medoxomil/Amlodipine/HCT Accord 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.

The summary of safety concerns proposed are the following:

Important identified risks	None
Important potential risks	None
Missing information	None

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for olmesartan-amlodipine-hydrochlorothiazide.

IV.4 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) 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 (used as a basis for bridging “key safety messages”), and

Solifenacin succinate 5/10mg film-coated tablets (used as a basis for bridging "Design/layout"). The bridging report submitted by the applicant has been found acceptable.

Based on the above justification the daughter PIL is considered comparable with the parent PILs and assessed as readable in compliance with Articles 59(3) and 61(1) of Directive 2001/83/EC as amended.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Olmesartan medoxomil/Amlodipine/HCT Accord is found adequate. There are no objections to the approval of Olmesartan medoxomil/Amlodipine/HCT Accord Edest from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

The results of studies 785-15, 0965-18, 0966-18 and 1035-16 with the 40/10/12.5 mg, 40/10/25, 40/5/12.5 mg and 40/5/25 mg formulation respectively can be extrapolated to the other strength 20/5/12.5 mg, according to conditions in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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
ES/H/0623/001-5/IA/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products Other variation	Yes	13-07-2020	Approved	N.A.
ES/H/0623/001-5/IB/002	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan Other variation	No	07-12-2021	Approved	N.A.
ES/H/0623/001-5/IA/003	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC Implementation of wording agreed by the competent authority	Yes	15-02-2022	Approved	N.A.
ES/H/0623/001-5/IA/004/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. • New certificate from an already	No	18-02-2022	Approved	N.A.

	approved manufacturer • New certificate from a new manufacturer (replacement or addition)				
ES/H/0623/001-5/IA/005	Other variation Update of SmPC and PIL information in-line with the wording of PRAC procedure outcome	Yes	06-04-2022	Approved	N.A.
ES/H/0623/001-5/IA/006	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC Implementation of wording agreed by the competent authority	Yes	05-08-2022	Approved	N.A.
ES/H/0623/001-5-IB/007	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	25-05-2023	Approved	N.A.
ES/H/0623/001-5/IA/008	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or	No	22-12-2023	Approved	N.A.

	quality control testing sites) All other				
ES/H/0623/001-5/IA/009	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product Minor change in the manu-facturing process	No	19-01-2024	Approved	N.A.
ES/H/0623/004/IA/010	Change in the batch size (including batch size ranges) of the finished product Up to 10-fold compared to the originally approved batch size	No	29-01-2024	Approved	N.A.
ES/H/0623/004/IA/011/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site • Primary packaging site	No	08-04-2024	Approved	N.A.
ES/H/0623/001-5/IA/012/G	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance Minor changes to an approved test procedure Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to	No No	27-06-2024	Approved	N.A.

	the relevant Ph. Eur. Monograph. Updated certificate from an already approved manufacturer				
ES/H/0623/001-5/R/001	Renewal	No	08-08-2024	Approved	N.A.
ES/H/0623/001-5/IA/013/G	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) All other Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. Deletion of certificates (in case multiple certificates exist per material)	No No	05-08-2024	Approved	N.A.
ES/H/0623/001-5/IB/014	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	Yes	27-03-2025	Not approved	Not available

ES/H/0623/001-5/IA/015	Other variation Update of SmPC and PIL information in-line with the wording of PRAC procedure outcome	Yes	07-02-2025	Approved	N.A.