

Public Assessment Report

Scientific discussion

Olmesartan/Amlodipine/ Hydrochlorothiazide Accord/Edest 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

**Olmesartan Medoxomil
Amlodipine Besilate
Hydrochlorothiazide**

ES/H/0623+0624/001-005/DC

Date: 26/05/2025

This module reflects the scientific discussion for the approval of Olmesartan/Amlodipine/Hydrochlorothiazide Accord/Edest 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 procedure was finalised on March 2020.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Olmesartan/Amlodipine/Hydrochlorothiazide 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 S.L.U. and for Olmesartan/Amlodipine/Hydrochlorothiazide Edest 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 Intas Third Party Sales 2005, S.L.

The product is indicated in the treatment of essential hypertension,

Add-on therapy

{Olmesartan Medoxomil/Amlodipine besilate/Hydrochlorothiazide 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 besilate/Hydrochlorothiazide 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 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/Hydrochlorothiazide film-coated tablets 20/5/12.5 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/Hydrochlorothiazide film-coated tablets 40/5/12.5 mg

Light yellow, round, bevel-edged, film-coated tablets debossed with “OC2” on one side and plain on other side.

Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide film-coated tablets 40/5/25 mg

Light yellow, oval, bevel-edged, film-coated tablets debossed with “OC3” on one side and plain on other side.

Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide film-coated tablets 40/10/12.5 mg

Brick red, round, bevel-edged, film-coated tablets debossed with “OC4” on one side and plain on other side.

Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide film-coated tablets 40/10/25 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/Hydrochlorothiazide tablets are packed in Alu-Alu blisters.

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

Description of the product

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

Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide film-coated tablets 20/5/12.5 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/Hydrochlorothiazide film-coated tablets 40/5/12.5 mg

Light yellow, round, bevel-edged, film-coated tablets debossed with “OC2” on one side and plain on other side.

Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide film-coated tablets 40/5/25 mg

Light yellow, oval, bevel-edged, film-coated tablets debossed with “OC3” on one side and plain on other side.

Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide film-coated tablets 40/10/12.5 mg

Brick red, round, bevel-edged, film-coated tablets debossed with “OC4” on one side and plain on other side.

Olmesartan medoxomil/Amlodipine/Hydrochlorothiazide film-coated tablets 40/10/25 mg

Brick red, oval, bevel-edged, film-coated tablets debossed with “OC5” on one side and plain on other side.

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/Hydrochlorothiazide tablets are packed in Alu-Alu blisters and/or PPCP (Polypropylen Co-Polymer) containers.

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.

Manufacture of the product

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.

Excipients

Excipients used are well known and of appropriate quality.

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.

Product specification, analytical procedures, batch analysis

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.

Container closure system

The finished product is 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

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.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

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

III.2 Environmental Risk Assessment (ERA)

Since Olmesartan/Amlodipine/Hydrochlorothiazide Accord/Edest 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.

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 is 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 C_{max} 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 C_{max} 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-∞} (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-∞} (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 $\pm$ 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 $\pm$ 1.0523	3.777 $\pm$ 1.0336
AUC ₀₋₇₂ (ng.h/mL)	123.750 $\pm$ 39.0109	126.715 $\pm$ 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-∞}	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-∞}	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/Hydrochlorothiazide /Amlodipine 40 mg/10 mg/12.5 mg film-coated tablets, when compared with the Reference Product Sevikaar HCT® 40 mg/10 mg/12.5 mg film-coated tablets in fasting condition seems to meet the bioequivalence criteria with respect to the C_{max} 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 C_{max} 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 C_{max} 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-∞} (ng.h/mL)	13945.386 ± 3965.5287	13987.707 ± 4283.5114
λ _z (1/h)	0.087 ± 0.0150	0.088 ± 0.0149
t _{1/2} (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-∞} (ng.h/mL)	1440.897 ± 337.5881	1388.601 ± 392.5894
λ _z (1/h)	0.079 ± 0.0077	0.078 ± 0.0082
t _{1/2} (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-∞}	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-∞}	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/Hydrochlorothiazide /Amlodipine 40 mg/10 mg/25 mg film-coated tablets, when compared with the Reference Product Sevikaar HCT® 40 mg/10 mg/25 mg film-coated tablets in fasting condition seems to meet the bioequivalence criteria with respect to the C_{max} 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 C_{max} 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 C_{max} 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 $\pm$ 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 $\pm$ 453.6721	1901.095 $\pm$ 483.0652
AUC _{0-t} (ng.h/mL)	12306.110 $\pm$ 3212.3058	12648.887 $\pm$ 3215.7913
AUC _{0-∞} (ng.h/mL)	12449.048 $\pm$ 3281.1301	12808.583 $\pm$ 3341.6847
λ _z (1/h)	0.088 $\pm$ 0.0150	0.089 $\pm$ 0.0146
t _½ (h)	8.193 $\pm$ 1.9796	8.084 $\pm$ 1.8899
AUC_%Extrap_obs (%)	1.099 $\pm$ 1.1133	1.113 $\pm$ 1.2349

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

Hydrochlorothiazide

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

Parameters (Units)	Mean $\pm$ 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 $\pm$ 20.6261	93.324 $\pm$ 27.0705
AUC _{0-t} (ng.h/mL)	621.541 $\pm$ 142.0455	644.283 $\pm$ 168.4212
AUC _{0-∞} (ng.h/mL)	641.360 $\pm$ 141.1780	665.331 $\pm$ 169.0912
λ _z (1/h)	0.082 $\pm$ 0.0114	0.082 $\pm$ 0.0118
t _½ (h)	8.598 $\pm$ 1.1001	8.574 $\pm$ 1.1107
AUC_%Extrap_obs (%)	3.268 $\pm$ 1.1651	3.324 $\pm$ 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)%			
lnC _{max}	1796.953	1842.435	97.5	90.16 - 105.50	22.2	99.8
lnAUC _{0-t}	11913.563	12271.962	97.1	90.54 - 104.09	19.6	100.0
lnAUC _{0-∞}	12046.747	12411.027	97.1	90.56 - 104.03	19.5	100.0

Hydrochlorothiazide

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-∞}	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/Hydrochlorothiazide /Amlodipine 40 mg/5 mg/12.5 mg film-coated tablets, when compared with the Reference Product Sevkar HCT® 40 mg/5 mg/12.5 mg film-coated tablets in fasting condition seems to meet the bioequivalence criteria with respect to the C_{max} 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 C_{max} 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 C_{max} 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-∞} (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 $\pm$ 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 $\pm$ 51.8177	209.497 $\pm$ 64.8298
AUC _{0-t} (ng.h/mL)	1435.734 $\pm$ 338.8126	1407.918 $\pm$ 328.4534
AUC _{0-∞} (ng.h/mL)	1470.075 $\pm$ 350.0507	1441.741 $\pm$ 340.5641
λ _z (1/h)	0.073 $\pm$ 0.0068	0.074 $\pm$ 0.0073
t _½ (h)	9.586 $\pm$ 0.8854	9.494 $\pm$ 0.9106
AUC_%Extrap_obs (%)	2.293 $\pm$ 0.7229	2.297 $\pm$ 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 $\pm$ 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 $\pm$ 0.4560	2.736 $\pm$ 0.5051
AUC ₀₋₇₂ (ng.h/mL)	109.679 $\pm$ 19.1000	110.497 $\pm$ 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 $\pm$ 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 $\pm$ 0.3252	1.327 $\pm$ 0.3628
AUC ₀₋₇₂ (ng.h/mL)	45.070 $\pm$ 14.4227	44.597 $\pm$ 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-∞}	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-∞}	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/Hydrochlorothiazide /Amlodipine 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/amlodipine/hydrochlorothiazide 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/Amlodipine/ Hydrochlorothiazide Edest 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:

<i>Important identified risks</i>	<i>None</i>
<i>Important potential risks</i>	<i>None</i>
<i>Missing information</i>	<i>None</i>

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/Amlodipine/Hydrochlorothiazide Accord/Edest is found adequate. There are no objections to the approval of Olmesartan/Amlodipine/Hydrochlorothiazide 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 the study (ies) with the <xxxx mg> strength (s) can be extrapolated to the <xxxx mg> strength (s), according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.