IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Olmesartan/Hydrochlorothiazide Clonmel 40 mg/12.5 mg film-coated tablets
Olmesartan medoxomil
Hydrochlorothiazide
PA0126/260/003

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Olmesartan/Hydrochlorothiazide Clonmel 20mg/12.5mg, 20mg/25mg, 40mg/12.5mg & 40mg/25mg Film-Coated Tablets, from Clonmel Healthcare Ltd.
The product is indicated for:

- Treatment of essential hypertension.
- Olmesartan/Hydrochlorothiazide Clonmelfixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on olmesartan medoxomil alone.

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 Olmetec Plus 20 mg / 12.5 mg, 20 mg / 25 mg, 40 mg / 12.5 mg,
40 mg / 25 mg, Daiichi Sankyo Europe GmbH 81366 München**.**
The original product is registered since 2005-05-12.
The concerned member states (CMS) involved in this procedure were Austria, Spain, Finland, and Portugal.
The marketing authorisation has been granted pursuant to Article of Directive 2001/83/EC.

II. QUALITY ASPECTS

I.1 Introduction

The application is for olmesartan/hydrochlorothiazide 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg and 40 mg/25 mg film-coated tablets.

I.2 Drug Substance

The active substances are olmesartan medoxomil and hydrochlorothiazide which are established active substances described in the European Pharmacopoeia (Ph. Eur.), and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).
The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specifications has been provided.

I.3 Medicinal Product

P.1 Composition
Each film-coated tablet contain either 20 mg and 12.5 mg, 20 mg and 25 mg, 40 mg and 12.5 mg or 40 mg and 25 mg of olmesartan medoxomil and hydrochlorothiazide respectively. The excipients in the medicinal product are listed in section 6.1 of the SmPC. A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European Guidelines.

P.3 Manufacture of the Product
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.
The manufacturing process has been validated according to relevant European guidelines.

P.4 Control of Other Substances (Excipients)
All ingredients comply with the requirements of the Ph. Eur. or an appropriate specification.

P.5 Control of the Finished Product
The Finished Product Specification is based on European guidelines, and the tests and control limits are considered appropriate for this type of product.
The analytical methods used are described in detail and are supported by validation data.
Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging Material
The approved packaging for this product is described in section 6.5 of the SmPC.
Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

I.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of olmesartan/hydrochlorothiazide 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg and 40 mg/25 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

I.1 Ecotoxicity/environmental risk assessment (ERA)

Since olmesartan/hydrochlorothiazide 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 Olmetec Plus, 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

I.1 Introduction

Olmesartan medoxomil and hydrochlorothiazide HCT are both well-known active substances with established efficacy and tolerability, as monotherapies or as a combination formulation.
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 a pilot bioequivalence study and 3 pivotal bioequivalence studies, which are discussed below.

I.2 Pharmacokinetics

Pilot Bioequivalence Study
A single-dose, three-treatment, three-period pilot bioequivalence study of two batches of Olmesartan HCT 40/25 mg tablets and Olmetec Plus® was conducted.
12 healthy male subjects were randomised to receive either Test 1 or Test 2 or Reference after an overnight fasting. The subjects were confined to hospital from 13 hours prior to 12 hours after drug administration.
A 7-day washout period separated the treatment periods.
Results

Table 2.1.4.3: Bioequivalence evaluation of Olmesartan/HCT 40/25 mg film-coated tablets in 107B12 / CT-37220-12-0117

Olmesartan			
Pharmacokinetic parameter	**Geometric Mean Ratio % T1/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	105.21	94.67 – 116.93	12.82
$AUC_{(0-\infty)}$	104.75	94.58 – 116.00	12.38
C_{max}	103.76	90.39 – 119.09	16.78
Pharmacokinetic parameter	**Geometric Mean Ratio % T2/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	98.18	88.34 – 109.11	12.82
$AUC_{(0-\infty)}$	97.94	88.44 – 108.47	12.38
C_{max}	93.83	81.75 – 107.70	16.78
Hydrochlorothiazide			
Pharmacokinetic parameter	**Geometric Mean Ratio % T1/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	99.20	89.91 – 109.46	11.93
$AUC_{(0-\infty)}$	98.67	89.39 – 108.90	11.97
C_{max}	105.41	92.02 – 120.76	16.54
Pharmacokinetic parameter	**Geometric Mean Ratio % T2/R**	**Confidence Intervals %**	**CV %**
$AUC_{(0-t)}$	99.20	89.90 – 109.45	11.93
$AUC_{(0-\infty)}$	98.96	89.66 – 109.22	11.97
C_{max}	101.77	88.83 – 116.58	16.54

As the 90 % confidence intervals were within the 80-125 limits bioequivalence was demonstrated.

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

1st Pivotal bioequivalence study:
Bioequivalence study of olmesartan and hydrochlorothiazide after single dose administration (fasting conditions) of Olmesartan/HCT 40/25 mg film-coated tablets (Test product) and Olmetec Plus® 40 mg/ 25 mg (Reference product) in 30 healthy subjects. There was a washout period of 7 days which is of sufficient duration.

Results
Olmesartan

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of olmesartan (N = 30)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	96.15	101.07	106.23	11.39
$AUC_{(0-\infty)}$	95.91	100.74	105.81	11.22
C_{max}	95.80	100.79	106.05	11.61

LCL = lower 90 %-confidence limit

UCL = upper 90 %-confidence limit

For the extent of absorption (AUC) and the rate of absorption (C_{max}) the confidence interval lies within the acceptance range of 80.00 % to 125.00 %.

Hydrochlorothiazide

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of hydrochlorothiazide (N = 30)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	89.08	94.55	100.35	13.62
$AUC_{(0-\infty)}$	89.30	94.74	100.50	13.50
C_{max}	77.62	84.31	91.57	18.99

LCL = lower 90 %-confidence limit

UCL = upper 90 %-confidence limit

For the extent of absorption (AUC) the confidence interval lies within the acceptance range of 80.00 % to 125.00 %. For the rate of absorption (C_{max}) the lower confidence limit slightly exceeds the lower limit of the acceptance range.

In summary it is concluded that for the extent of absorption (AUC) bioequivalence could be accepted for both Olmesartan and hydrochlorothiazide, the rate of absorption ($C_{max)}$ could be accepted for Olmesartan, but for the rate of absorption ($_{Cmax}$) bioequivalence could not be accepted for hydrochlorothiazide.
Further explanation was provided by the company as to the reasons for this bioequivalence failing to meet the C_{max} limit in the 1st pivotal study conducted with the test formulation in the 40/25 mg strength. Following a review it was concluded that the reference batch used is to be considered as an extreme batch with regards to initial HCT dissolution. In line with the guideline requirement that it has to be ensured that a representative batch of the reference product should be used for a BE study.

Second Pivotal bioequivalence study 2

Bioequivalence study of olmesartan and hydrochlorothiazide after single dose administration (fasting conditions) of Olmesartan/HCT 40/25 mg film-coated tablets (Test product) and Olmetec Plus® 40 mg/25 mg (Reference product) in 42 healthy subjects.
Wash-out period: at least 7 days

Results

Olmesartan

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of olmesartan (N = 42)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	93.26	99.47	106.09	17.68
$AUC_{(0-\infty)}$	93.18	99.26	105.74	17.34
C_{max}	92.73	99.43	106.61	19.16

LCL = lower 90 %-confidence limit

UCL = upper 90 %-confidence limit

Hydrochlorothiazide

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of hydrochlorothiazide n (N = 42)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	94.60	99.24	104.10	13.08
$AUC_{(0-\infty)}$	94.67	99.14	103.83	12.61
C_{max}	91.57	97.66	104.16	17.68

LCL = lower 90 %-confidence limit

UCL = upper 90 %-confidence limit

This study demonstrated bioequivalence to the reference medicinal product as the 90 percent confidence intervals were demonstrated to meet the predefined limits in accordance with bioequivalence guidelines.

Third bioequivalence study:

This study was conducted to demonstrate bioequivalence for the Olmesartan 20 mg hydrochlorothiazide 25 mg formulation.

A single-dose, two-treatment, two-period pilot bioequivalence study of two batches of Olmesartan HCT 20/25 mg tablets and Olmetec Plus® was conducted.

42 healthy male subjects were randomised to receive either Test 1 or Test 2 or Reference after an overnight fasting with a wash out of 7 days.

The combined results are shown below.

Calculated 90 %-confidence intervals, geometric mean ratios (T/R) and CV_{res} (%) from the OLS analysis of olmesartan (N = 42)

Parameter	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
$AUC_{(0-t)}$	94.58	99.48	104.63	13.81
C_{max}	90.35	96.72	103.54	18.71

LCL = lower 90 %-confidence limit

UCL = upper 90 %-confidence limit

The geometric mean values for $AUC_{(0-t)}$ for olmesartan were determined after administration of the test product as 3601.0 ng/ml·h and after administration of the reference product as 3619.9 ng/ml·h. The geometric mean maximum plasma concentrations (C_{max}) for olmesartan were determined after administration of the test product as 571.8 ng/ml and after administration of the reference product as 591.2 ng/ml. Maximum plasma concentrations were reached for olmesartan after 2.33 h (arithmetic mean value) for the test product and after 2.04 h (arithmetic mean value) for the reference product. Median of t_{max} values for olmesartan is 2.13 h for the test product and 2.00 h for the reference product.

For the extent of absorption (AUC) and the rate of absorption (C_{max}) the 90%- confidence interval lies within the acceptance range of 80.00 % to 125.00 %.

In summary, it is concluded that the test product is bioequivalent to the reference product regarding olmesartan.

*ln-transformed values

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

HPRA 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).

I.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/hydrochlorothiazide.

- Summary table of safety concerns as approved in RMP

Summary of safety concerns

Important identified risks

Important potential risks

Missing information

· Hypersensitivity · Renal impairment · Hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia · Moderate and severe hepatic impairment, cholestasis and biliary obstructive disorders · 2nd and 3rd trimester of pregnancy · Combined use of renin-angiotensin-system (RAS)-acting agents leading to increased risk of hyperkalaemia (high blood potassium levels), low blood pressure and kidney failure, compared with using one RAS-acting agent alone. · Lithium toxicity with concomitant use of olmesartan/hydrochlorothiazide · Sprue-like enteropathy
· Potential interaction with medicinal products affecting potassium levels · Increased risk of fatal events from cardiovascular causes in patients with type 2 diabetes with additional cardiovascular risks · Acute myopia, secondary acute angle-closure glaucoma
· Use in paediatric patients

For all of the safety concerns routine pharmacovigilance activities and routine risk minimisation measures are acceptable.

I.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Olmetec Plus. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product.
Risk management is adequately addressed.
This generic medicinal product can be used instead of the reference product.

The package leaflet 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 PIL was English.
The results show that the package leaflet 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.

V. OVERALL CONCLUSIONS

The quality of the medicinal product is acceptable and no new non clinical or clinical safety concerns have been identified. The applicant has demonstrated bioequivalence to the reference product Olmetec Plus in accordance with bioequivalence guidelines (CPMP/EWP/QWP/1401/98 Rev.1Corr). There is extensive clinical experience with Olmesartan and hydrochlorothiazide as a combination which supports the therapeutic value of this medicinal product.
The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.
There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Olmesartan medoxomil/ Hydroichlorothiazide with the reference product Olmetec Plus, and have therefore granted a marketing authorisation.
The decentralised procedure was finalised with a positive outcome on 23/12/15.