IPAR

Public Assessment Report

Scientific discussion

Olmesartan Medoxomil Clonmel 10mg, 20mg, 40mg film-coated tablets
Olmesartan Medoxomil

IE/H/446/001-003/DC

Date: 23/12/15

This module reflects the scientific discussion for the approval of Olmesartan Medoxomil Clonmel 10mg, 20mg, 40mg film-coated tablets. The procedure was finalised at 23/12/15. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Olmesartan Medoxomil Clonmel 10mg, 20mg, 40mg film-coated tablets, from Clonmel Healthcare Ltd.

The product is indicated for;

- Treatment of essential hypertension in adults.
- Treatment of hypertension in children and adolescents from 6 to less than 18 years of age.

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 10 mg, 20 mg and 40 mg film-coated tablets from Daiichi Sankyo Europe GmbH Germany and marketed for more than 10 years in most countries of the European Community. The original product is registered since 2002/08/13.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Spain, Finland,

France, Italy, Lithuania, Netherlands 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 medoxomil 10 mg, 20 mg and 40 mg film-coated tablets.

I.2 Drug Substance

The active substance is olmesartan medoxomil an established active substance described in the European Pharmacopoeia (Ph. Eur.), and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specification has been provided.

I.3 Medicinal Product

P.1 Composition

Each film-coated tablet contain either 10 mg, 20 mg or 40 mg of olmesartan medoxomil. 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.

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 10 mg, 20 mg and 40 mg film-coated tablets.

III NON-CLINICAL ASPECTS

I.1 Ecotoxicity/environmental risk assessment (ERA)

Since Olmesartan medoxomil 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, 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 is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

I.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Olmesartan medoxomil Glenmark 40 mg (Glenmark Pharmaceuticals Europe Ltd., UK) is compared with the pharmacokinetic profile of the reference product Olmetec 40 mg film-coated tablets (Daiichi Sankyo Europe GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Biowaiver</u>

A biowaiver is requested for the 10 and 20 mg film-coated tablets. The MAH was asked to justify comparative

dissolution tests at pH 4.5. The applicant provided further data which demonstrated comparable dissolution behaviour between the biobatch (40 mg) and the strengths for which a biowaiver has been applied for. Where the dissolution is not comparable (numerically) at pH 4.5, this has been explained by solubility of olmesartan medoxomil at this pH. Therefore the biowaiver for the 10 mg and 20 mg tablet can be granted.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 subjects male and female subjects, aged between 21 and 52 years.

Each subject received a single dose (40 mg) of one of the 2 olmesartan medoxomil formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours.

There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at analysis pre-dose (within 60 min) and 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 24.00, 36.00 and 48.00 hours after drug administration.

The design of the study is acceptable. The wash-out period, the sampling period and sampling scheme were adequate to estimate pharmacokinetic parameters of olmesartan.

As olmesartan medoxomil can be taken irrespective of food, a study under fasting conditions is considered appropriate.

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.

The selection of olmesartan as the primary pharmacokinetic parameter to establish bioequivalence is considered appropriate as olmesartan medoxomil is completely metabolised to the pharmacologically active metabolite, olmesartan, by esterases in the gastrointestinal mucosa, portal blood and liver.

Standard pharmacokinetic variables were analysed.

Results

Thirty subjects completed the trial successfully.

Pharmacokinetic parameters (geometric mean values; N = 30)

Parameter		olmesartan
$AUC_{(0-t)}$ (ng/ml·h)	T	5984.1
	R	5982.0
C_{max} (ng/ml)	T	885.3
	R	905.7

T = Test product

R = Reference product

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

Parameter	LCL 90 (%)	Ratio (%)	UCL 90 (%)	CV_{res} (%)
$AUC_{(0-t)}$	92.52	100.04	108.17	17.93
C_{max}	90.62	97.75	105.44	17.38

LCL 90 = lower 90 %-confidence limit

UCL 90 = upper 90 %-confidence limit

AUC0-t area under the plasma concentration-time curve from time zero to t hours

Cmax maximum plasma concentration

Conclusion on bioequivalence study

The 90% confidence intervals calculated are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Olmesartan medoxomil 40 mg is considered bioequivalent with Olmetec 40 mg film-coated tablets.

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 medoxomil.

Summary table of safety concerns as approved in RMP

Summary of safety concerns

Important identified risks

- Fetotoxicity upon olmesartan exposure in 2nd and/or 3rd trimester of pregnancy
- Hyperkalaemia
- Increase in adverse effects risk in patients with biliary obstructive disorde
- Concomitant treatment with other renin-angiotensin system(RAS)-acting agent(s)
- Lithium toxicity during concomitant use with olmesartan
- Sprue-like enteropathy

Important potential risks

- Potential interaction with medicinal products affecting potassium levels
- Use in the sub-populations with renal artery, atortic, or mitrial valve steno

Missing information

- Use in paediatric patients
- Use in patients with severe renal and/or hepatic impairment

For all 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. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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. The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

V OVERALL CONCLUSIONS

Olmesartan medoxomil 10 mg, 20 mg and 40 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Olmetec 10 mg, 20 mg and 40 mg film-coated tablets. Olmetec is a well-known medicinal product with an established favourable efficacy and safety profile.
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 in accordance with bioequivalence guidelines (CPMP/EWP/QWP/1401/98 Rev.1Corr).

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 with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23/12/15.