CBG MEB

Public Assessment Report

Scientific discussion

Olmesartan medoxomil Glenmark 10 mg, 20 mg and 40 mg film-coated tablets

(olmesartan medoxomil)

NL/H/3128/001-003/DC

Date: 1 February 2016

This module reflects the scientific discussion for the approval of Olmesartan medoxomil Glenmark 10 mg, 20 mg and 40 mg film-coated tablets. The procedure was finalised on 8 May 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Olmesartan medoxomil Glenmark 10 mg, 20 mg and 40 mg film-coated tablets from Glenmark Pharmaceuticals Europe 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 (NL License RVG 28782-28784) which has been registered in the Netherlands by Daiichi Sankyo Nederland B.V. since 27 May 2003 through mutual recognition procedure DE/H/0384/001-003.

The concerned member states (CMS) involved in this procedure were Germany, Ireland, Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Olmesartan medoxomil Glenmark 10 mg is a white to off white, round film-coated tablet, debossed with 476 on one side and plain on the other side with a characteristic odour
Olmesartan medoxomil Glenmark 20 mg is a white to off white, round film-coated tablet, debossed with 437 on one side and plain on the other side with a characteristic odour, approx. 8.6 mm in diameter.
Olmesartan medoxomil Glenmark 40 mg is a white to off white, oval-shaped film-coated tablet debossed with 438 on one side and plain on the other side with a characteristic odour, approx.15.3 mm in length and 7.2 mm in breadth.

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

The excipients are:
Tablet core - cellulose microcrystalline, low substituted hydroxypropyl cellulose, lactose monohydrate, cellulose microcrystalline, hydrogenated castor oil, magnesium stearate
Coating - hypromellose, hydroxypropyl cellulose, titanium dioxide, talc

The tablets are dose proportional.

II.2 Drug Substance

The active substance is olmesartan medoxomil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is slightly soluble in ethanol (96%) and practically insoluble in water and in heptane. The solubility in water is pH dependent. The active substance has no asymmetric carbons. The manufactured form is crystalline. The polymorphic form is routinely controlled.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality

and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The described manufacturing process of olmesartan medoxomil comprises four synthetic steps. The drug substance is sufficiently characterized with regard to chemical structure and polymorphic form. One well-defined crystalline form is consistently manufactured. The provided information on potential genotoxic impurities is considered acceptable.

Quality control of drug substance
The proposed drug substance specification comprises the specifications of the Ph. Eur. monograph with additional tests for residual solvents, one starting material and polymorphism, adopted from the ASMF holder, with additional tests and requirements for particle size distribution and microbial quality. The particle size distribution specification has been set based on the particle size distribution of the active substance batch used for the manufacture of the test bio-batch. Results of batch analysis have been provided of three batches, demonstrating compliance with this specification.

Stability of drug substance
Stability data on the active substance have been provided for five production-scale batches stored at 25°C/60% RH (three batches up to 60 months, one batch up to 24 months) and three batches at 40°C/75% RH (six months).
No significant changes were observed in the currently available stability data. The granted re-test period is 48 months without specific storage condition.

II.3 Medicinal Product

Pharmaceutical development
The formulation development is straightforward based on the composition of the reference product. The polymorphic form is routinely controlled. Consistency of the form over manufacture and 6-month storage has been demonstrated and is also adequately controlled by the dissolution test. As a fixed composition and manufacturing process is applied, the compact development is appropriate.
The proposed dissolution test and specification (not less than 80% (Q) in 15 min) is acceptable. The bio-waivers for the 10 mg and 20 mg tablets are justified from a chemical-pharmaceutical perspective.

Manufacturing process
The drug product is prepared by conventional wet granulation process followed by compression and coating. Purified water is used as granulation fluid. The various steps of the manufacturing process, the process parameters, and the in-process controls have been adequately described. The submitted validation on small scale batches is sufficient, as the process is considered a standard manufacturing process.

Control of excipients
For the coating an in-house specification is applied. The individual components of the coating comply with their Ph.Eur. monograph. For the other excipients reference is made to the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identity, average weight, dissolution, water content, uniformity of dosage units, assay, degradation (purity), and microbiological quality. The finalized specifications at release and shelf-life are considered acceptable. Results of batch analysis have been provided of three batches per strength, demonstrating compliance with the specification.

Stability of drug product
Results of stability studies are available covering 12 months storage at 25°C/60%RH and 6 months at 40°C/75%RH). In the stability studies there were no significant changes in appearance or assay, dissolution, related substances, water content and microbial quality. Therefore, based on the 12 months long-term results, the shelf-life can be extrapolated to 24 months in Alu-Alu blister without specific storage condition. It has been demonstrated that the tablets are photostable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose monohydrate, no materials of animal and/or human origin are contained or used in the manufacturing process of the medicinal product. TSE safety of the lactose has been confirmed by the supplier.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Olmesartan medoxomil Glenmark has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Olmesartan medoxomil Glenmark 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

IV.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.

IV.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.

Biowaiver
A biowaiver is requested for the 10 and 20 mg film-coated tablets. Due to the reported low solubility of olmesartan medoxomil at pH 4.5 the MAH could not demonstrate similar dissolution at this pH for the

10 mg strength. The MAH was asked to submit additional comparative dissolution tests at pH 4.5 comparing one 40 mg tablet vs four 10 mg tablets to demonstrate that the different dissolution profiles can be attributed to substance related poor solubility and not to formulation related differences. The requested data were submitted. Furthermore, additional comparative dissolution tests at pH 4.5 comparing one 40 mg tablet vs two 20 mg tablets were also submitted. It is agreed that the dissolution profiles of the Olmesartan medoxomil Glenmark 40 mg tablet versus 4x10 mg tablets and 2x20 mg tablets are very similar after visual inspection. The olmesartan medoxomil tablets comply to all other biowaiver requirements. Therefore the biowaiver for the 10 mg and 20 mg tablet can be granted.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-55 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 15 days.

Blood samples were collected pre-dose and at 0.16, 0.33, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.33, 3.67, 4.0, 4.33, 4.67, 5.0, 5.5, 6, 8, 10, 12, 18, 24, 36 and 48 hours after administration of the products.

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-nine subjects completed the trial successfully, as one subject discontinued from the study on his own accord.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan under fasted conditions.

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	97144 ± 3048	9929 ± 3111	1370 ± 418	2.75 (1.00 - 4.67)	--
Reference	10175 ± 3095	10408.39 ± 3155	1439 ± 455	2.25 (1.25 - 4.33)	--
***Ratio (90% CI)**	0.95 (0.89- 1.02)	0.95 (0.89-1.02)	0.96 (0.87-1.05)	--	--
CV (%)	19	19	25	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Olmesartan medoxomil Glenmark 40 mg is considered bioequivalent with Olmetec 40 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Olmesartan medoxomil Glenmark.

- Summary table of safety concerns as approved in RMP

Important identified risks	Symptomatic hypotension (especially in volume depleted patients) Dual renin-angiotensin system blockade Hyperkalaemia Impaired renal function Foetal and neonatal toxicity associated with use during pregnancy Sprue-like enteropathy
Important potential risks	Rhabdomyolysis Decrease in haemoglobin and/or haematocrit
Missing information	Paediatric use in children <18 years of age Use during lactation Use in patients with severe hepatic impairment Use in patients with severe renal impairment.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product 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.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The MAH submitted a justification for not submitting the results of a readability test. The content of the package leaflet of the

product applied for is comparable to the package leaflet of Telmisartan/Hydrochlorothiazide. A comparison of the key safety messages is presented to argue that the contents (key safety messages) of the package leaflet is comparable to the package leaflet of Telmisartan/Hydrochlorothiazide. The reasoning for bridging regarding contents is accepted as the safety messages in the PL are comparable to that of Telmisartan/Hydrochlorothiazide, which has successfully been user tested.
The reasoning for bridging with regard to design and lay out is also accepted, as the design and layout of the PL are comparable to the design and layout of the leaflet of Telmisartan/Hydrochlorothiazide.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Olmesartan medoxomil Glenmark 10 mg, 20 mg and 40 mg 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

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Olmesartan medoxomil Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 May 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached