CBG MEB

Public Assessment Report

Scientific discussion

Olmesartan Medoxomil/Hydrochloorthiazide Accord 20/12.5 mg, 20/25 mg, 40/12.5, and 40/25 mg, film-coated tablets

(olmesartan medoxomil/hydrochlorothiazide)

NL/H/3765/001-004/DC

Date: 28 November 2017

This module reflects the scientific discussion for the approval of Olmesartan Medoxomil/Hydrochloorthiazide Accord 20/12.5 mg, 20/25 mg, 40/12.5, and 40/25 mg, film-coated tablets. The procedure was finalised on 4 May 2017. 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/Hydrochloorthiazide Accord 20/12.5 mg, 20/25 mg, 40/12.5, and 40/25 mg, film-coated tablets, from Accord Healthcare Limited.

The product is indicated for the treatment of essential hypertension. This fixed 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 HCTZ 20/12.5 mg, 20/25 mg, 40/12.5 mg and 40/25 mg, film-coated tablets (NL License RVGs 32740, 32741, 104240 and 104241) which has been registered in the Netherlands by Daiichi Sankyo Nederland B.V since 4 December 2006 through MRP DE/H/0523/001-004.

The concerned member states (CMS) involved in this procedure were Austria, Spain, Finland, Ireland, Italy 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/Hydrochloorthiazide Accord consists in four different strengths:

- 20/12.5 mg: reddish-yellow, round, film-coated tablets, debossed with “OH1” on one side and plain on the other side.
- 20/25 mg: pinkish, round, film-coated tablets, debossed with “OH4” on one side and plain on the other side.
- 40/12.5 mg: reddish-yellow, oval, film-coated tablets, debossed with “OH2” on one side and plain on the other side.
- 40/25 mg: pinkish, oval film-coated tablets, debossed with “OH3” on one side and plain on the other side.

Each tablet contains 20 mg or 40 mg olmesartan medoxomil and 12.5 or 25 mg hydrochlorothiazide.

The film-coated tablets are packed in Alu-Alu blisters or Alu-Alu perforated unit dose blisters.

The excipients are:
Tablet core - hydroxyl propyl cellulose, lactose monohydrate, cellulose microcrystalline, low substituted hydroxyl propyl cellulose and magnesium stearate.
Tablet coating – hypromellose, titanium dioxide (E171), macrogol 3000, talc, yellow iron oxide (E172) and red iron oxide (E172).

The cores of the tablet strengths 20/12.5 mg and 40/25 mg are fully dose proportional. The cores of the tablets strengths 20/25 mg and 20/12.5 mg are identical except for the amount of 12.5 mg hydrochlorothiazide which is corrected with the same amount of filler lactose. Likewise, the cores of the tablet strengths 40/12.5 mg and 40/25 mg are identical except for the amount of 12.5 mg hydrochlorothiazide which is corrected with the same amount of filler lactose.

II.2 Drug Substances

The active substances are olmesartan medoxomil and hydrochlorothiazide and both well known active substances described in the European Pharmacopoeia (Ph. Eur.).

Olmesartan medoxomil is a white or almost white crystalline powder and practically insoluble in water, slightly soluble in ethanol (96%) and practically insoluble in heptane. The active drug substance does exhibit polymorphism, however one polymorphic form is consistently produced.
Hydrochlorothiazide is a white or almost white, crystalline powder. It is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol (96%). No polymorphism has been reported till date as per literature available.

The CEP procedure is used for both active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
Both active substance specifications are considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEPs with additional specifications for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for 2 batches of each substance.

Stability of drug substance
Olmesartan medoxomil is stable for 5 years and hydrochlorothiazide for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
Olmesartan Medoxomil/Hydrochloorthiazide Accord is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The excipients of the drug product are usual for immediate release solid oral drug product. The drug product formulations largely follow the reference product.
Two bioequivalence studies are performed; one with the 40/12.5 mg strength and one with the 20/25 mg strength. The products used in the bioequivalence studies are acceptable. The strengths tested in the bioequivalence studies are the extreme batches of the four strength concerning ratio active substances to excipients and ratio active substances to each other. For the other two strengths, 20/12.5 mg and 40/25 mg, a biowaiver was applied for. Dissolution data to support the biowaivers have been provided. Overall, the pharmaceutical development is acceptable.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. A standard wet granulation method is used. Process validation data on the product have been presented for 3 pilot scaled batches for each strength, in accordance with the relevant European guidelines.

Control of excipients
All excipients, except the film-coating, comply with monographs of several Pharmacopeia. In-house specifications are applied for the two coatings mixtures Opadry beige and Opadry pink. For the solid components of the coating mixtures reference is made to the US-NF for iron oxide and to the Ph Eur for the other components. For methylene chloride reference is made to the US-NF. For Low-substituted Hydroxypropyl Cellulose reference is made to the USP. Certificates of analysis are provided for each excipient. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight, related substances, loss on drying, residual solvents, assay, uniformity of dosage units, dissolution, microbial

quality and identification. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data 3 batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 batches of each strength stored at 25°C/60% RH (18 months) and 40°C/75%RH (6 months). The storage conditions were in accordance with applicable European guidelines. No significant trends or changes were observed. The stability studies showed that the product is photostable. On basis of the data submitted, a shelf life was granted of 24 months without any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. The manufacturer has confirmed that it does not have potential risk for TSE/BSE and it is derived from milk, sourced from healthy animals in the same conditions as milk collected for human consumption and is prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev3.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Olmesartan Medoxomil/Hydrochloorthiazide Accord 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/Hydrochloorthiazide Accord 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 HCTZ 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 and hydrochlorothiazide are well-known active substances 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profiles of the test products Olmesartan Medoxomil/Hydrochloorthiazide Accord 20/25 mg and 40/12.5 mg, film-coated tablets (Accord Healthcare Ltd, the United Kingdom) are compared with the pharmacokinetic profiles of the reference product Olmetec HCTZ 20/25 mg and 40/12.5 mg (Daiichi Sankyo Nederland B.V., the Netherlands).

The choice of the reference product in the bioequivalence studies is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

For the strengths 20/12.5 mg and 40/25 mg a biowaiver was applied for and could be granted based on the following:

- Olmesartan Medoxomil/Hydrochlorothiazide 20/12.5 mg, 20/25 mg, 40/12.5 mg, 40/25 mg film-coated tablets are manufactured at the same manufacturing site as the reference product.
- Olmesartan medoxomil and hydrochlorothiazide demonstrate linear pharmacokinetics over the therapeutic dose range.
- The qualitative compositions of all four strengths is the same
- The four strengths are not dose-proportional. The MAH however used a bracketing approach, i.e. the bioequivalence studies were performed with two strengths representing the extremes (the two strengths differing most in composition). This is considered acceptable.
- In-vitro dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Bioequivalence studies

Study I: Olmesartan Medoxomil/Hydrochloorthiazide Accord 20 mg/25 mg, film-coated tablets

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy subjects. Each subject received a single dose (20 mg/25 mg) of one of the 2 Olmesartan medoxomil/hydrochlorothiazide 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 13 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.333, 3.667, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. Olmesartan medoxomil and hydrochlorothiazide may be taken without reference to food intake, therefore a study under fasted conditions is considered acceptable.

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.

Results

One subject withdrew from the study on his own accord. A second subject was withdrawn on medical grounds. Therefore, 54 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=54	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	6587.7 ± 1691	6684.3 ± 1729	1011.2 ± 215	2.00 (1.25 - 5.00)
Reference	6348.5 ± 1708	6434 ± 1742	919.5 ± 214	2.00 (1.00 – 5.00)

***Ratio (90% CI)**	1.04 (0.99 – 1.09)	1.04 (0.99 – 1.09)	1.10 (1.06 – 1.15)	--
$AUC_{0-\infty}$ 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				

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=54	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1607.2 ± 378	1644 ± 391	233.5 ± 60	2.00 (0.750 - 5.017)
Reference	1518.8 ± 331	1552.5 ± 346	231.4 ± 74	2.00 (0.75 – 5.00)
***Ratio (90% CI)**	1.06 (1.02 – 1.09)	1.06 (1.02 – 1.09)	1.02 (0.97 – 1.08)	--
$AUC_{0-\infty}$ 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				

**ln-transformed values*

Study II: Olmesartan Medoxomil/Hydrochloorthiazide Accord 40 mg/12.5 mg, film-coated tablets

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy subjects. Each subject received a single dose (40 mg/12.5 mg) of one of the 2 olmesartan medoxomil/hydrochlorothiazide 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 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.333, 3.667, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36 and 48 after administration of the products.

The design of the study is acceptable. Olmesartan medoxomil and hydrochlorothiazide may be taken without reference to food intake, therefore a study under fasted conditions is considered acceptable.

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.

Results

One subjects withdrew from the study on his own accord. Therefore, a total of 55 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of olmesartan under fasted conditions.

Treatment N=55	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	11247.8 ± 2673	11399.6 ± 2741	1556.1 ± 342	2.25 (1.2 - 3.7)
Reference	10937.9± 2763	11086.3 ± 2831	1486.5 ± 353	2.50 (1.0 - 4.5)
***Ratio (90% CI)**	1.04 (0.99 – 1.08)	1.04 (0.99 – 1.08)	1.05 (1.01 – 1.10)	--

$AUC_{0-\infty}$	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

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=55	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	778.6 ± 210	800.7 ± 212	116.6 ± 34	1.75 (0.7 - 4.5)
Reference	779.1 ± 202	802.9 ± 205	117.3 ± 36	2.00 (0.7 - 4.5)
***Ratio (90% CI)**	1.00 (0.96 – 1.03)	1.00 (0.96 – 1.03)	1.00 (0.96 – 1.04)	--

$AUC_{0-\infty}$	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

**ln-transformed values*

Conclusion on bioequivalence studies:
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 studies Olmesartan Medoxomil/Hydrochloorthiazide Accord is considered bioequivalent with Olmetec HCTZ

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/Hydrochloorthiazide Accord.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Foetotoxicity • Sprue-like enteropathy • Hypotension, • Hyperkalaemia • Dual renin-angiotensin system blockade. • Fluid or Electrolyte imbalance
Important potential risks	• Renal impairment • Elevation of liver function values • Hypersensitivity reactions incl. angioedema and serum sickness • Decrease in haemoglobin and/or haematocrit • Increased cardiovascular mortality in patients with type 2 diabetes
Missing information	• Use in children and adolescents below 18 years of age • Use during breast feeding • Severe hepatic 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 HCTZ . 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.

V. USER CONSULTATION

The MAH submitted a justification for not submitting the results of a readability test. In this justification, the MAH states that the content of the package leaflet of the product applied for is comparable to the package leaflet of the innovator product containing olmesartan medoxomil and hydrochlorothiazide. A comparison of the key safety messages is presented to argue that the content (key safety messages) of the package leaflet is comparable to the package leaflet of Olmesartan medoxomil /Hydrochlorothiazide.

With regard to the design and layout, the MAH submitted a bridging statement explaining that the design and layout of the Package Leaflet of Olmesartan Medoxomil/Hydrochloorthiazide Accord are comparable to the design and layout of the Package Leaflet of Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC), which has successfully been user tested.
The MAH has provided the assessment of this user test. Therefore bridging is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Olmesartan Medoxomil/Hydrochloorthiazide Accord 20/12.5 mg, 20/25 mg, 40/12.5, and 40/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of product Olmetec HCTZ 20/12.5 mg, 20/25 mg, 40/12.5 mg and 40/25 mg. Olmetec HCTZ 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/Hydrochloorthiazide Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 May 2017.

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