CBG MEB

# Public Assessment Report

# Scientific discussion

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

# (olmesartan medoxomil)

## NL/H/3188/001-003/DC

## Date: 4 August 2016

**This module reflects the scientific discussion for the approval of Olmesartan medoxomil Jubilant 10mg, 20mg and 40mg film-coated tablets. The procedure was finalised on 17 June 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 Jubilant 10 mg, 20 mg and 40 mg film-coated tablets, from Jubilant Pharmaceuticals n.v.

The product is indicated for treatment of essential hypertension. 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 28782-4) 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 Cyprus, Denmark, Sweden and the UK.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Olmesartan medoxomil Jubilant is a film-coated tablet.

- the 10 mg tablets are white, circular film-coated tablets of approximately 6.6 mm diameter and 3.3 mm thickness, debossed with “C9” on one side. Each 10 mg film-coated tablet contains 10 mg olmesartan medoxomil.
- the 20 mg tablets are white, circular film-coated tablets of approximately 8.6 mm diameter and 3.85 mm thickness, debossed with “D1” on one side. Each 20 mg film-coated tablet contains 20 mg olmesartan medoxomil.
- the 40 mg tablets are white, oval film-coated tablets of approximately 4.95 mm thickness, 15.25 mm length and 7.15 mm width, debossed with “466” on one side. Each 40 mg film-coated tablet contains 40 mg olmesartan medoxomil.

The product is packed in laminated OPA/aluminum/PVC/aluminum blister packs.

The excipients are:

*Tablet core*
- Cellulose, microcrystalline
- Lactose monohydrate
- Hydroxypropylcellulose
- Low substituted hydroxypropylcellulose
- Magnesium stearate

*Tablet coat*
- Titanium dioxide (E 171)
- Talc
- Hypromellose
- Hydroxypropylcellulose

The three tablet strengths are fully dose proportional.

## II.2 Drug Substance

The active substance is olmesartan medoxomil, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Olmesartan medoxomil is classified as BCS class II drug (low solubility and high permeability). Hence it is slightly soluble in ethanol and practically insoluble in water and in heptane. The solubility in water is pH dependent. The active substance has no asymmetric carbons. It has been demonstrated that the same crystalline polymorphic form is manufactured consistently.

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 from two intermediates and one starting material. Both intermediates are prepared in three steps from two starting materials. Sufficient information has been given related to the starting materials: the suppliers are laid down, the synthesis routes of the starting materials are provided, and adequate specifications for the starting materials are presented.

Quality control of drug substance
The proposed drug substance specification comprises the specification of the Ph.Eur., with additional tests for residual solvents, one starting material, potential genotoxic impurities and polymorphism defined by the ASMF holder, and with additional test and requirements for particle size distribution. The specification is considered acceptable. The limits set for the various parameters are acceptable. Sufficient batch analysis data have been provided, demonstrating compliance with the specification.

Stability of drug substance
Stability data on the active substance have been provided in accordance with applicable European guidelines 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 (6 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 development of the product has been described, the choice of excipients is justified and their functions explained. Consistency of the polymorphic form over manufacture and storage has been demonstrated. As a fixed composition and manufacturing process is applied, the development is appropriate.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Olmesartan medoxomil Jubilant 40 mg tablets and reference product, Olmetec 40 mg tablets obtained from Germany. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. Sufficient comparative dissolution data between the test and reference product have been provided.

For the lower strengths a biowaiver is requested. The 10 mg, 20 mg and 40 mg tablets are fully dose proportional film-coated tablets and are manufactured using the same manufacturing process. Comparative dissolution data in media with different pH (1.2, 4.5, and 6.8) between 40 mg tablets and the other two strengths (10 mg and 20 mg) have been provided. The results show that the all three tablet strengths have comparable dissolution characteristics throughout the physiological pH range. A biowaiver of strengths based on the provided dissolution data was granted for the 10 mg and 20 mg tablets.

Manufacturing process
The drug product is prepared by a conventional wet granulation process followed by compression and coating. The various steps of the manufacturing process, the process parameters, and the in-process controls have been adequately described. The submitted validation on minimum production scale batches is sufficient, as the process is considered a standard manufacturing process. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients and their quantities used are common and comply with the Ph.Eur or other pharmacopeia. For the coating an in-house specification is applied; the individual components of the coating comply with their Ph.Eur. monographs.

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, identity, tablet dimensions, dissolution, loss on drying, uniformity of dosage units, assay, degradation (purity), and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Batch analytical data from sufficient batches have been provided, demonstrating compliance with the specification.

Stability of drug product
Results of stability studies cover 18 months (one batch of each strength) at 25°C/60% RH, 12 months storage at 25°C/60% RH, and 6 months storage at 40°C/75% RH. The major trend observed is an increase in degradation products, which is covered by the release and end-of shelf-life limits. Olmesartan, the pharmacologically active metabolite, is the main degradation product in all cases. The tablets are photo-stable. In view of the data submitted, the proposed shelf-life of two years, when stored below 25°C/60% RH can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Except for lactose monohydrate and magnesium stearate 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. The lactose is produced from milk that has been sourced from healthy cows in the same conditions as milk collected for human consumption and has been prepared without the use of other ruminant material than calf rennet.
For magnesium stearate a copy of the TSE CEP has been provided.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Olmesartan medoxomil Jubilant 10 mg, 20 mg and 40 mg tablets have 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 Jubilant 10 mg, 20 mg and 40 mg tablets are 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.

The MAH has submitted a bioequivalence study for Olmesartan medoxomil Jubilant 40 mg. For the other strengths (10 mg and 20 mg) a biowaiver is applied for. Both the bioequivalence study and the biowaiver are discussed below.

## IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Olmesartan medoxomil Jubilant 40 mg film-coated tablets (Jubilant Pharmaceuticals N.V., Belgium) 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*
The choice of the reference product in the bioequivalence study is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Biowaiver*
The MAH has carried out the bioequivalence studies on the highest strength (40 mg). A biowaiver is requested for other strengths (10 mg and 20 mg) as olmesartan medoxomil exhibits linear kinetics in the studied dose range and as all the following general biowaiver criteria are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths
- Appropriate *in vitro* dissolution data confirms the adequacy of waiving:
    - Dissolution tests have been performed in pH 1.2, pH 4.5 acetate buffers and a pH 6.8 phosphate buffer. Sufficient dissolution profiles at pH 1.2 and 6.8 have been submitted. Due to the reported low solubility of olmesartan medoxomil at pH 4.5 the MAH performed additional data showing sufficient comparable dissolution at pH 4.5 regardless of formulation.

Olmesartan medoxomil Jubilant 10 mg and 20 mg tablets comply with the general requirements for a biowaiver. Therefore a biowaiver for these strengths was granted.

*Design*
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male and female subjects, aged 22-42 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 a 10 hour overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.0, 3.5, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post-dose under monochromatic light in each study period. Samples at 48 and 72 hours post-dose were collected on ambulatory basis.

The design of the study is acceptable and in line with pharmacokinetic properties of olmesartan medoxomil; the sampling time schedule and wash-out period are adequate taking into account the elimination half-life of the drug. Olmesartan has linear pharmacokinetics, therefore the conduct of the bioequivalence study at the highest strength (40 mg) is acceptable. Olmesartan medoxomil tablets can be taken irrespective of food intake; therefore the single dose study under fasting conditions is 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*
Three subjects were withdrawn from the study due to adverse events and therefore samples were not collected at all time points. Two subjects experienced pyrexia in period I and one subject experienced vomiting in period II. A total of 25 subjects were included in the pharmacokinetic and statistical analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of olmesartan medoxomil under fasted conditions.**

| **Treatment N=25** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-\infty}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| Test | 8165.71 ±2201.00 | 8269.38 ±2210.93 | 1287.91 ±258.69 | 1.75 (1.25 - 3.50) | 7.2 ± 1.1 |
| **Reference** | 7984.09 ±1877.60 | 8079.69 ±1882.90 | 1267.28 ±275.88 | 1.75 (1.00-3.50) | 7.1 ± 1.3 |
| ***Ratio (90% CI)** | 1.01 (0.95 - 1.08) | 1.01 (0.95 - 1.08) | 1.02 (0.95 - 1.10) | -- | -- |
| **CV (%)** | 13.69 | 13.66 | 14.69 | -- | -- |

**$AUC_{0-\infty}$** 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 Jubilant 40 mg film-coated tablets 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 Jubilant.

Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | • Hyperkalaemia<br>• Foetotoxicity<br>• Hypotension<br>• Sprue-like enteropathy |
| Important potential risks | • Renal impairment<br>• Elevation of liver function values<br>• Hypersensitivity including angioedema and serum sickness<br>• Decrease in haemoglobin and/or haematocrit<br>• CV risks in patients with type 2 diabetes<br>• Rhabdomyolysis |
| Missing information | • Use in children and adolescents below 18 years<br>• Use during lactation<br>• Use in 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 film-coated tablets. No new clinical studies were conducted. Bioequivalence of the 40 mg strength with the originator has been proven and a biowaiver for the other strengths (10 mg and 20 mg) can be granted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

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. Eighteen questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Olmesartan medoxomil Jubilant 10 mg, 20 mg and 40 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Olmetec 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 Jubilant with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 June 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 |
|---|---|---|---|---|---|---|
| Update of the SPC and PL in line with the innovator and Paediatric Assessment report (UK/W/0021/PDWS/001) | NL/H/3188/IB/001/G | IB | 22/04/2016 | 06/07/2016 | Approved | |
| Replace ASMF with CEP from an already approved manufacturer (R0-CEP 2012-228-Rev02)<br><br>Addition of 2 parameters to the specification of the active substance:<br>• Content of 4-chloromethyl -5-methyl-[1,3] dioxol -2-one by HPLC<br>• Particle Size (By Malvern mastersizer) | NL/H/3188/IB/002/G | IB | 25/05/2016 | 23/06/2016 | Approved | |