Public Assessment Report

UK PAR

Olmesartan 10 mg film-coated tablets
Olmesartan 20 mg film-coated tablets
Olmesartan 40 mg film-coated tablets

(olmesartan medoxomil)

UK Licence No: PL 36884/0007-0009

Morpharma Limited
Lay Summary

Olmesartan 10 mg film-coated tablets
Olmesartan 20 mg film-coated tablets
Olmesartan 40 mg film-coated tablets
(olmesartan medoxomil)

This is a summary of the Public Assessment Report (PAR) for Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets (PL 36884/0007-0009). It explains how the applications for Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets were assessed and their authorisations recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets. For practical information about using Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The products may be referred to as ‘Olmesartan film-coated tablets’in this report.

What are Olmesartan film-coated tablets and what are they used for?
Olmesartan film-coated tablets are ‘generic’ medicines’. This means that Olmesartan film-coated tablets are similar to ‘reference medicines’ already authorised in the UK called Olmetec 10 mg, 20 mg and 40 Film-coated Tablets (PL 08265/0015-0017; Daiichi Sankyo UK Limited). Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (PL 08265/0015-0017; Daiichi Sankyo UK Limited) may be referred to as Olmetec Film-coated Tablets in this report.

Olmesartan film-coated tablets are used for the treatment of high blood pressure (also known as ‘hypertension’). High blood pressure can damage blood vessels in organs such as the heart, kidneys, brain and eyes. In some cases this may lead to a heart attack, heart or kidney failure, stroke or blindness. Usually high blood pressure has no symptoms. It is important to have your blood pressure checked to prevent damage occurring.

High blood pressure can be controlled with medicines such as Olmesartan film-coated tablets. The patient’s doctor will probably also recommended that the patient make some changes in his/her lifestyle to help lower the blood pressure (for example losing weight, giving up smoking, reducing the amount of alcohol drunken and reducing the amount of salt in the diet). The doctor may also urge the patient to take regular exercise, such as walking or swimming. It is important that the patient follows this advice from his/her doctor.

How do Olmesartan film-coated tablets work?
Olmesartan film-coated tablets contain the active ingredient, olmesartan medoxomil, which belongs to a group of medicines called angiotensin-II receptor antagonists. They lower blood pressure by relaxing the blood vessels.

How are Olmesartan film-coated tablets used?
Olmesartan film-coated tablets are taken by mouth. The tablets can be taken with or without food. The tablets should be swallowed with a sufficient amount of water (e.g. one small glassful). If possible, the patient should take his/her daily dose at the same time each day, for example at breakfast.

The tablets should always be taken exactly as advised by the doctor or pharmacist. The patient should check with a doctor or pharmacist if he/she is not sure.

The recommended starting dose is 10 mg once a day. However, if the patient’s blood pressure is not
controlled, the doctor may decide to change the patient’s dose up to 20 mg or 40 mg once a day, or prescribe additional medicines. In patients with mild to moderate kidney disease, the dose will not be higher than 20 mg once a day.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Olmesartan film-coated tablets can only be obtained with a prescription.

What benefits of Olmesartan film-coated tablets have been shown in studies?
As Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to their respective reference medicines, Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (Daiichi Sanko Spain, S.A., Spain). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are possible side effects of Olmesartan film-coated tablets?
Because Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets are generic medicines that are considered bioequivalent to the reference medicines, Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (Daiichi Sanko Spain, S.A., Spain), the benefits and possible side effects are taken as being the same as the respective reference medicines.

For the full list of all side effects reported with Olmesartan film-coated tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Olmesartan film-coated tablets approved?
It was concluded that, in accordance with EU requirements, Olmesartan film-coated tablets have been shown to have comparable quality and to be bioequivalent to Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (Daiichi Sanko Spain, S.A., Spain). Therefore, the MHRA decided that, as for Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (Daiichi Sanko Spain, S.A., Spain), the benefits outweigh the identified risks and recommended that Olmesartan film-coated tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Olmesartan film-coated tablets?
A Risk Management Plan has been developed to ensure that Olmesartan film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Olmesartan film-coated tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Olmesartan film-coated tablets
Marketing Authorisations were granted for Olmesartan film-coated tablets (PL 36884/0007-0009) to Morpharma Limited on 13 January 2016.

The full PAR for Olmesartan film-coated tablets follows this summary.
For more information about treatment with Olmesartan film-coated tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2016.
SCIENTIFIC DISCUSSION

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Scientific discussion

I  INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Morpharma Limited Marketing Authorisations for the medicinal products Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets (PL 36884/0007-0009) on 13 January 2016. These are Prescription Only Medicines (POM) indicated in the treatment of essential hypertension.

These applications were submitted in accordance to Article 10(1) of Directive 2001/83/EC, as amended, as generic applications. Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets cross-refer to the reference products Olmetec 10 mg, 20 mg and 40 Film-coated Tablets (Daiichi Sankyo Europe GmbH, Germany). The corresponding reference products in the UK are Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (PL 08265/0015-17; Daiichi Sankyo UK Limited), which were first authorised in the UK on 22 May 2003.

The active ingredient, olmesartan medoxomil, is an angiotensin II receptor antagonist. Olmesartan medoxomil is a prodrug, which is hydrolysed to olmesartan during absorption from the gastrointestinal tract.

A single-dose, bioequivalence study was submitted to support these applications comparing the applicant’s test product Olmesartan 40 mg film-coated tablets with the reference product Olmetec 40 mg Film-coated Tablets (Daiichi Sankyo Spain, S.A., Spain) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets outweigh the risks and Marketing Authorisations were granted.

II  QUALITY ASPECTS
II.1  Introduction
These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications cross-referring to Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (Daiichi Sankyo). The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Olmesartan 10 mg film-coated tablets are pink, circular, biconvex, film-coated tablets, of approximate 7.1 mm diameter and 3.0 mm thickness, debossed with 'E' on one side and '10' on the other.

Olmesartan 20 mg film-coated tablets are pink, circular, biconvex, film-coated tablets, of approximate 8.8 mm diameter and 3.9 mm thickness, debossed with 'B' on one side and '767' on the other.

Olmesartan 40 mg film-coated tablets are pink, oval, biconvex, film-coated tablets, of approximate 15.6 mm length, 8.1 mm width and 5.0 mm thickness, debossed with ‘B’ on one side and ‘768’ on the other.

Each tablet contains 10 mg, 20 mg or 40 mg of the active ingredient, olmesartan medoxomil.
The tablets also contain microcrystalline cellulose, lactose monohydrate, hydroxypropylcellulose, low substituted hydroxypropylcellulose and magnesium stearate in the tablet cores and hypromellose, titanium dioxide (E171), polyethylene glycol, talc and red iron oxide (E172) in the film-coatings.

Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in aluminium/aluminium blisters placed into cardboard boxes, in a pack size of 28 film-coated tablets.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE
Olmesartan medoxomil
INN: Olmesartan medoxomil
Chemical Name: 5-methyl-2-oxo-2H-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-{4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-imidazole-5-carboxylate
Molecular formula: C_{29}H_{30}N_{6}O_{6}
M_{r}: 558.6
Structure:

\[
\text{\includegraphics[width=0.5\textwidth]{structure.png}}
\]

Appearance: White or almost white crystalline powder
Solubility: Practically insoluble in water; slightly soluble in ethanol (96 percent), practically insoluble in heptane
Polymorphism: Polymorphism has been cited in the literature
Isomerism: Olmesartan medoxomil does not exhibit isomerism.

Olmesartan medoxomil is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.
Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable, film-coated tablets that could be considered generic medicinal products of the reference products Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (Daiichi Sanko Europe GmbH, Germany). Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution profiles have been provided for these products and the respective reference products. The dissolution profiles were satisfactory.

With the exception of low substituted hydroxypropylcellulose and red iron oxide (E172), all excipients comply with their respective European Pharmacopoeia monographs. Low substituted hydroxypropylcellulose is controlled to a suitable in-house specification. Red iron oxide (E172) is in compliance with its National Formulary specification and the current EU Directive concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data that comply with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months has been accepted. These medicinal products do not require any special temperature storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.
II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for these applications for Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets.

II.5 Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PIL are available on the MHRA website. The current labelling is presented below:
The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up livery to the regulatory authorities for approval before packs are marketed.

**Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets:**

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</th>
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</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Olmesartan 10 mg film-coated tablets
Olmesartan 20 mg film-coated tablets
Olmesartan 40 mg film-coated tablets
Olmesartan medoxomil

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 10 mg olmesartan medoxomil
Each film-coated tablet contains 20 mg olmesartan medoxomil
Each film-coated tablet contains 40 mg olmesartan medoxomil

3. **LIST OF EXCIPIENTS**

Contains lactose. See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

Film-coated tablet.
Blister pack of 28 tablets.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

None

8. **EXPIRY DATE**

EXP MM/YYYY

9. **SPECIAL STORAGE CONDITIONS**

None

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

None
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Morpharma Ltd, Elms Lane, Wembley, Middx HA0 2NN, UK

12. MARKETING AUTHORISATION NUMBER(S)

(For Olmesartan 10 mg film-coated tablets) - PL 36884/0007
(For Olmesartan 20 mg film-coated tablets) - PL 36884/0008
(For Olmesartan 40 mg film-coated tablets) - PL 36884/0009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription (POM)

15. INSTRUCTIONS ON USE

Use as directed by the physician.
Read the package leaflet before use.

16. INFORMATION IN BRAILLE

Olmesartan 10 mg
Olmesartan 20 mg
Olmesartan 40 mg
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### BLISTER

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan 10 mg film-coated tablets</td>
</tr>
<tr>
<td>Olmesartan 20 mg film-coated tablets</td>
</tr>
<tr>
<td>Olmesartan 40 mg film-coated tablets</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
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<tbody>
<tr>
<td>Morpharma Ltd</td>
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</tbody>
</table>

<table>
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<tr>
<th>3. EXPIRY DATE</th>
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<tr>
<td>EXP MM/YYYY</td>
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<tr>
<th>4. BATCH NUMBER</th>
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<tr>
<td>Lot</td>
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<table>
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<tr>
<th>5. OTHER</th>
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</table>
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of olmesartan medoxomil are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental exposure to olmesartan medoxomil is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of olmesartan medoxomil is well-known.

These are generic applications as defined by Article 10(1) of Directive 2001/83/EC, as amended, with the reference products Olmetec 10 mg, 20 mg and 40 mg Film-coated Tablets (Daiichi Sanko Europe GmbH, Germany). In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted a bioequivalence study comparing the applicant’s test product Olmesartan 40 mg film-coated tablets with the reference product Olmetec 40 mg Film-coated Tablets (Daiichi Sanko Spain, S.A., Spain) under fasting conditions to support the applications;

With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

IV.2 Pharmacokinetics
The clinical pharmacokinetic properties of olmesartan medoxomil are well-known.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study.
A randomised, open label, two-treatment, two-sequence, single-dose, crossover, oral bioequivalence study comparing the pharmacokinetics of the applicant’s test product Olmesartan 40 mg film-coated tablets (Morpharma Limited, UK) and the reference product Olmetec 40 mg Film-coated Tablets (Daiichi Sanko Spain, S.A., Spain) in healthy, adult male and female subjects under fasting conditions.

The subjects were administered one 40 mg tablet of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Fasting continued for at least 4 hours following drug administration. Blood samples were collected before and up to and including 36 hours after each administration. The washout period between the treatment phases was a minimum of 7 days. The pharmacokinetic results are presented below.

### Table 1: Summary statistics for pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>1785.462 ± 463.8542</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.hr/mL)</td>
<td>12666.077 ± 3195.1370</td>
</tr>
<tr>
<td>$AUC_{0-\text{inf}}$ (ng.hr/mL)</td>
<td>13054.773 ± 3308.3430</td>
</tr>
<tr>
<td>AUC_Extrapolated (%)</td>
<td>2.92 ± 1.216</td>
</tr>
</tbody>
</table>

* Median and Range values reported for $T_{\text{max}}$

$C_{\text{max}}$: maximum plasma concentration

$AUC_{0-t}$: area under the plasma concentration-time curve from time zero to $t$ hours

$AUC_{0-\text{inf}}$: area under the plasma concentration-time curve from time zero to infinity

SD: standard deviation

### Table 2: Pharmacokinetic parameters (geometric least square means, ratios and confidence intervals [CI]) of olmesartan

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Geometric Least Squares Means (Test,T)</th>
<th>Geometric Least Squares Means (Ref,R)</th>
<th>Ratio (T/R) (%)</th>
<th>90% Confidence Limits (T vs. R)</th>
<th>Intra Subject CV %</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Lu(C_{\text{max}})$ (ng/mL)</td>
<td>1728.6071</td>
<td>1916.7298</td>
<td>90.19</td>
<td>(84.73, 95.99)</td>
<td>16.67</td>
<td>99.99</td>
</tr>
<tr>
<td>$Lu(AUC_{0-t})$ (ng.hr/mL)</td>
<td>12253.9981</td>
<td>12707.0941</td>
<td>96.45</td>
<td>(90.92, 102.32)</td>
<td>15.77</td>
<td>100.00</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$: maximum plasma concentration

$AUC_{0-t}$: area under the plasma concentration-time curve from time zero to $t$ hours

Ratios and 90% CI calculated from log-transformed data

The 90% confidence intervals of the test/reference ratio for $C_{\text{max}}$ and $AUC_{0-t}$ lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Thus, the data support the claim that the applicant’s test product, Olmesartan 40 mg film-coated tablets, is bioequivalent to the reference product, Olmetec 40 mg Film-coated Tablets (Daiichi Sanko Spain, S.A., Spain), under fasting conditions.

As the 10 mg, 20 mg and 40 mg strength tablets of the product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 40 mg tablet strength can be extrapolated to the 10 mg and 20 mg strength tablets.
IV.3 Pharmacodynamics
The clinical pharmacodynamic properties of olmesartan medoxomil are well-known. No new pharmacodynamics data were submitted and none are required for applications of this type.

IV.4 Clinical Efficacy
The clinical efficacy of olmesartan medoxomil is well-known. No new efficacy data are presented for applications of this type.

IV.5 Clinical Safety
With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for applications of this type. The safety profile of olmesartan medoxomil is well-known. No new or unexpected safety issues were raised during the bioequivalence study.

IV.6 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 10 mg, 20 mg and 40 mg film-coated tablets.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Renal insufficiency and renal failure</th>
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<tr>
<td></td>
<td>Hypotension-related events</td>
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<td></td>
<td>Foetotoxicity</td>
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<td>Biliary obstruction</td>
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<tr>
<td></td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>Raised creatine phosphokinase, hypertriglyceridaemia and hyperuricaemia</td>
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<tr>
<td>Important potential risks</td>
<td>Lithium toxicity</td>
</tr>
<tr>
<td>Missing information</td>
<td>Pregnancy and lactation</td>
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<td></td>
<td>Paediatric population</td>
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<tr>
<td></td>
<td>Renal impairment and kidney transplantation</td>
</tr>
<tr>
<td></td>
<td>Hepatic impairment</td>
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</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation activities are acceptable to monitor the safety concerns described in the Risk Management Plan.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets.

V. USER CONSULTATION
A user consultation with target patient groups on the package information leaflets have been performed on the basis of a bridging report making reference to the user tested Patient Information Leaflet for the product, Olmesartan Distriquimica 10mg, 20mg and 40mg film-coated tablets, in Spain. The bridging report submitted by the applicant has been found to be acceptable.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Olmesartan 10 mg, 20 mg and 40 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. As the pharmacokinetics, pharmacodynamics and toxicology of olmesartan medoxomil are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s test product Olmesartan 40 mg film-coated tablets and the reference product Olmetec 40 mg Film-coated Tablets (Daiichi Sankyo Spain, S.A., Spain) under fasting conditions.

As the 10 mg, 20 mg and 40 mg strength tablets of the product meet the criteria for a biowaiver specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the results and conclusions from the bioequivalence study with the 40 mg tablet strength can be extrapolated to the 10 mg and 20 mg strength tablets.

SAFETY
The safety profile of olmesartan medoxomil is well-known. No new or unexpected safety issues or concerns arose from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling text are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with olmesartan medoxomil is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of Marketing Authorisations is recommended.
Olmesartan 10 mg film-coated tablets
Olmesartan 20 mg film-coated tablets
Olmesartan 40 mg film-coated tablets

(olmesartan medoxomil)

PL 3684/0007-0009

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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