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LAY SUMMARY

The MHRA granted Neolab Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets (PL 08137/0225-7) on 12 July 2013.

These prescription-only medicines (POM) are used to lower blood pressure in people with high blood pressure (hypertension); to protect the kidney in type 2 diabetic patients with laboratory evidence of impaired renal function and proteinuria ≥ 0.5 g per day (a condition in which urine contains an abnormal amount of protein); to treat patients with chronic heart failure when therapy with specific medicines called angiotensin-converting enzyme inhibitors (ACE inhibitors) is not considered suitable; and to decrease the risk of stroke in patients with high blood pressure and thickened heart muscle.

Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets belong to a group of medicines known as angiotensin-II receptor blockers (ARBs). Losartan can reduce blood pressure and improve the ability of the heart to pump blood.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
LOSARTAN POTASSIUM 25 MG FILM-COATED TABLETS
LOSARTAN POTASSIUM 50 MG FILM-COATED TABLETS
LOSARTAN POTASSIUM 100 MG FILM-COATED TABLETS
PL 08137/0225-7

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Neolab Limited Marketing Authorisations (licences) for the medicinal products Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets (PL 08137/0225-7) on 12 July 2013.

These are prescription-only medicines (POM) indicated for the treatment of essential hypertension in adults and in children and adolescents 6-18 years of age; renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day; and chronic heart failure in adult patients when treatment with Angiotensin Converting Enzyme (ACE) inhibitors is not considered suitable due to incompatibility or contraindication. It is also indicated for the reduction of the risk of stroke in adult hypertensive patients with left ventricular hypertrophy.

These applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal products of the originator products Cozaar 25 mg, 50 mg & 100 mg Film-coated Tablets (Merck, Sharp and Dohme Ltd), which were initially granted licences in the UK on 15 December 1994 (25 mg and 50 mg) and 28 November 2001 (100 mg). The reference product used in the bioequivalence study is Cozaar 50 mg Film-coated Tablets (Merck, Sharp and Dohme Ltd, UK).

These products contain the active ingredient losartan potassium. Losartan is a specific angiotensin-II receptor (type AT_1) antagonist. Angiotensin II binds to the AT_1 receptor, which is found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle proliferation. In vitro and in vivo, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis.

No new non-clinical studies were conducted, which is acceptable given that the application is a generic application based on an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is a generic application based on an originator product that has been licensed for over 10 years.

A bioequivalence study was performed, which compared the pharmacokinetics of Losartan Potassium 50 mg Film-coated Tablets with those of Cozaar 50 mg Film-coated Tablets (Merck, Sharp and Dohme Ltd, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP)

The MHRA has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of these products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Losartan potassium

INN: Losartan potassium
Chemical name: (i) 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl]-imidazole-5-methanol monopotassium salt
(ii) 2-n-butyl-4-chloro-5-hydroxymethyl-1-[(2’-1H-tetrazol-5-yl)biphenyl-4-yl)methyl] imidazole monopotassium salt

Structure:

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
\text{CH}_2\text{OH} & \\
\text{N} & \quad \text{NN}
\end{align*}
\]

Molecular formula: C_{22}H_{22}ClKN_{6}O
Molecular weight: 461.01
Physical form: White or almost white crystalline powder, which is freely soluble in water and slightly soluble in acetonitrile.

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance losartan potassium.

Synthesis of the drug 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 for the active substance. 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. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
DRUG PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients, as follows:
Tablet Core: Microcrystalline cellulose, dibasic calcium phosphate, colloidal anhydrous silica, croscarmellose sodium, talc, magnesium stearate

Film-coating: Opadry white 31F58914, which contains hypromellose (E464), lactose monohydrate, titanium dioxide (E171), polyethylene glycol 4000, sodium citrate dihydrate (E331).

Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets contain 2.12 mg, 4.24 mg and 8.48 mg potassium, respectively.

With the exception of the Opadry white 31F58914, which complies with suitable in-house standards, all excipients used comply with their respective European Pharmacopoeia monographs

None of the excipients used contain material of animal or human origin. The magnesium stearate used in the manufacture of the finished product is of vegetable origin.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce safe, tolerable tablets that could be considered generic medicinal products of the originator products Cozaar 25 mg, 50 mg & 100 mg Film-coated Tablets (Merck, Sharp and Dohme Ltd). The applicant has provided a suitable product development rationale and data.

Comparative in vitro dissolution profiles have been provided for the applicant’s products versus the reference products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

Process validation has been carried out on three production-scale batches of each finished product. The results are satisfactory.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container Closure System
The finished products are packaged in polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium blisters in a pack size of 28 film-coated tablets.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

Stability
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months, with the storage conditions of “Store in the original package in order to protect from light and moisture” and “Do not store above 25ºC”.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of losartan potassium are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A balanced, open-label, randomised, two-treatment, four-period, two-sequence, single-dose, replicate crossover bioequivalence study to compare the pharmacokinetic profile of Losartan Potassium 50 mg Film-coated Tablets (Test) with Cozaar 50 mg Film-coated Tablets (Reference) in healthy adult male subjects, under fasting conditions.

Study participants were given each treatment after a 10-hour fast. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 48 hours post dose. Each treatment regimen was separated by a 7-day washout period.

The main pharmacokinetic results are presented in the tables below:

Losartan – the geometric mean, %T/R and 90% confidence intervals of in-transformed pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Geometric mean</th>
<th>*(%)T/R</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>80</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>C_max (ng/ml)</td>
<td>253.73</td>
<td>291.97</td>
<td>86.22</td>
</tr>
<tr>
<td>AUC_{0-t} (hr.ng/ml)</td>
<td>551.35</td>
<td>571.69</td>
<td>96.33</td>
</tr>
<tr>
<td>AUC_{0-∞} (hr.ng/ml)</td>
<td>570.23</td>
<td>589.45</td>
<td>96.63</td>
</tr>
</tbody>
</table>

*T/R is ratio of TestGeoLSM/RefGeoLSM.

Carboxylic acid metabolite (E-3174) of Losartan – the geometric mean, %T/R and 90% confidence intervals of in-transformed pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Geometric mean</th>
<th>*(%)T/R</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>78</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
<td>C_max (ng/ml)</td>
<td>339.87</td>
<td>345.94</td>
<td>98.12</td>
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<tr>
<td>AUC_{0-t} (hr.ng/ml)</td>
<td>2841.83</td>
<td>2892.53</td>
<td>98.24</td>
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<tr>
<td>AUC_{0-∞} (hr.ng/ml)</td>
<td>2988.50</td>
<td>3187.52</td>
<td>96.35</td>
</tr>
</tbody>
</table>

*T/R is ratio of TestGeoLSM/RefGeoLSM.

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for AUC. Whilst the active metabolite C_max data is within the acceptable range, the 90% confidence interval for C_max for losartan potassium falls below the criteria for bioequivalence of 80.00-125.00 %. However, as the intra-individual variability is >30%, a pre-defined wider range of 75.00-
133.00% applies. Losartan Potassium 50 mg Film-coated Tablets can, therefore, be considered to be bioequivalent with Cozaar 50 mg Film-coated Tablets.

As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 50 mg strength can be extrapolated to the 25 mg and 100 mg strength tablets.

EFFICACY
No new data on efficacy have been submitted and none are required for this type of application

SAFETY
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
These are consistent with the SmPCs for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference products and is satisfactory.

LABELLING
This is satisfactory

APPLICATION FORMS (MAA)
These are satisfactory.

MEDICAL CONCLUSION
The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Losartan Potassium 25 mg, 50 mg and 100 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.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and Cozaar 50 mg Film-coated Tablets (Merck, Sharp and Dohme Ltd, UK). As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 50 mg strength can be extrapolated to the 25 mg and 100 mg Film-coated Tablets.

No new or unexpected safety concerns arose from these applications.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference products.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with losartan potassium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
# STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
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<th>The MHRA received the marketing authorisation applications on 01 April 2008.</th>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 11 April 2008.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 06 April 2010, 30 June 2010, 16 January 2012, 16 February 2012, 23 April 2012, 09 January 2013 and 03 May 2013.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 12 July 2013.</td>
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</table>
LOSARTAN POTASSIUM 25 MG FILM-COATED TABLETS
LOSARTAN POTASSIUM 50 MG FILM-COATED TABLETS
LOSARTAN POTASSIUM 100 MG FILM-COATED TABLETS
PL 08137/0225-7

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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</table>
Summary of Product Characteristics and Patient Information Leaflet

The current approved versions of the SmPCs and PIL are available on the MHRA website.

Labelling

Carton for 25 mg Film-coated Tablets:

Blister for 25 mg Film-coated Tablets:
UKPAR Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets

Carton for 50 mg Film-coated Tablets:

Blister for 50 mg Film-coated Tablets:
UKPAR Losartan Potassium 25 mg, 50 mg and 100 mg Film-coated Tablets

Carton for 100 mg Film-coated Tablets: