Public Assessment Report

Decentralised Procedure

Losartan Potassium 12.5 mg, 25 mg, 50 mg and 100 mg film-coated tablets

(Losartan potassium)

Procedure Number(s): UK/H/2670/001-004/DC

UK Licence No(s): PL 21880/0139-0142

Applicant: Medreich Limited
LAY SUMMARY

On the 18 January 2010 the MHRA granted Pharmakal Limited Marketing Authorisations (licences) Losartan Potassium 12.5mg, 25mg, 50mg and 100mg Film-coated Tablets (PL 20796/0008-0011; UK/H/2670/001-0004/DC). For ease of reading, the products may be referred to as Losartan Potassium in this Scientific discussion. These are prescription-only medicines (POM).

Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels, causing them to tighten. This results in an increased in blood pressure. Losartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure. Losartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

Losartan Potassium is used
- to treat patients with high blood pressure (hypertension) in adults and in children and adolescents 6-18 years of age.
- to protect the kidney in hypertensive 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, medicine used to lower high blood pressure) is not considered suitable by your doctor. If the patient’s heart failure has been stabilised with an ACE inhibitor they should not be switched to losartan.
- in patients with high blood pressure and a thickening of the left ventricle, Losartan has been shown to decrease the risk of stroke (“LIFE indication”).

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Losartan potassium 12.5 mg, 25 mg, 50 mg and 100 mg film-coated tablets outweigh the risks. Hence, Marketing Authorisations have been granted.

Subsequent to Change of Ownership (CoA) procedures on 09 May 2010, the Marketing Authorisations (PL 20796/0008-0011) were transferred to Helm AG (PL 20897/0067-70). The Marketing Authorisations were thereafter transferred to Medreich plc (PL 21880/0139-0142) on 31 August 2012.
# SCIENTIFIC DISCUSSION

## TABLE OF CONTENTS

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Introduction</td>
<td>Page 4</td>
</tr>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>Page 4</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>Page 7</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>Page 7</td>
</tr>
<tr>
<td>V</td>
<td>Overall conclusion and benefit/risk assessment and recommendation</td>
<td>Page 15</td>
</tr>
<tr>
<td></td>
<td>Steps taken after authorisation - Summary</td>
<td>Page 20</td>
</tr>
<tr>
<td></td>
<td>Annex 1</td>
<td>Page 21</td>
</tr>
</tbody>
</table>
Scientific discussion

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Losartan Potassium 12.5 mg, 25 mg, 50 mg and 100 mg Film-coated Tablets (PL 20796/0008-0011; UK/H/2670/001-0004/DC), in the treatment of hypertension, heart failure and diabetic renal disease, could be approvable.

These are applications for Losartan Potassium 12.5 mg, 25 mg, 50 mg and 100 mg Film-coated Tablets using the Decentralised Procedure. These were submitted on the basis of Directive 2001/83/EC (as amended) Article 10(1) generic application. The applicant claims that these are generic products to Cozaar® Tablets (Merck Sharp & Dohme). Cozaar® Tablets were first authorised in the UK in 1994 (PL: 00025/0324 & 36)

With the UK as the Reference Member State (RMS) in these Decentralised Procedure, Pharmakal Limited is applying for the Marketing Authorisation for Losartan Potassium 12.5 mg, 25 mg, 50 mg and 100 mg Film-coated Tablets in Germany and Italy.

Losartan is a synthetic oral angiotensin-II receptor (type AT₁) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT₁ receptor 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 cell proliferation.

The submitted dossier is of an acceptable standard.

The RMS 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 this product. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Subsequent to Change of Ownership (CoA) procedures on 09 May 2010, the Marketing Authorisations (PL 20796/0008-0011) were transferred to Helm AG (PL 20897/0067-70). Following a further CoA procedure, the Marketing Authorisations were thereafter transferred to Medreich plc (PL 21880/0139-0142) on 31 August 2012.

II. QUALITY ASPECTS

DRUG SUBSTANCE

INN: Losartan Potassium

Chemical Name: 2-Butyl-4chboro-1-[(2’-(1H-tetrazol-5-yl)[1,1’-biphenyl]-4-yl)methyl]-1H-imidazole-5-methanol, potassium salt; 2-Butyl-4chboro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-imidazole-5-methanol, monopotassium salt
Structure:

Molecular Formula: $C_{22}H_{22}ClKN_6O$

Molecular Weight: 461.0

Losartan potassium is a white or almost white crystalline powder, which is freely soluble in water and methanol and very slightly soluble in chloroform. It is also freely soluble in alkaline pH, but becomes practically insoluble at acidic pH (pH 6 and below).

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Losartan potassium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the drug substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided which support the re-test period.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, pregelatinised starch, magnesium stearate, water purified and opadry Y-1-7000 White.

All excipients comply with their respective European Pharmacopoeia monographs except Opadry Y-1-7000 White which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin. The lactose used is from Meggle and appropriate TSE documentation regarding sourcing has been supplied.
None of the other excipients are of human origin.

**Pharmaceutical Development**
Suitable pharmaceutical development data have been provided for these applications.

The aim of the development work was to produce a product demonstrating essential similarity to the innovator product (Cozaar®).

**Manufacture**
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on pilot scale batches of the product. The results are satisfactory.

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

**Container-Closure System**
The finished product is packed in PVC/ PVdC/PE/Aluminium blister packs.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years has been set, with no storage instructions.

**Bioequivalence/bioavailability**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

**SmPC, PIL, Labels**
The SmPC, 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. 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 it contains.

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

The requirements for a generic product of the originator product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator product.
III. NON-CLINICAL ASPECTS
No new non-clinical data have been supplied with this application. However, a non-clinical expert report summarising relevant non-clinical studies has been included in the dossier. This is satisfactory.

IV. CLINICAL ASPECTS
1. Introduction
1.1. Type of Application and Regulatory Background
These decentralised applications concern generic versions of losartan potassium, under Losartan potassium 12.5 mg, 25 mg, 50 mg and 100 mg Film-coated Tablets trade names. The originator product is Cozaar 25 mg, 50mg and 100mg film-coated tablets by Merck, Sharp & Dohme, registered since 1994.

With UK as the Reference Member State in these Decentralised Procedures, Pharmakal Ltd is applying for the Marketing Authorisations for Losartan potassium 12.5 mg, 25 mg, 50 mg and 100 mg Film-coated Tablets in Germany and Italy.

Losartan potassium is an Angiotensin-II (AT\textsubscript{1}) receptor blocker that is used for control of hypertension as monotherapy or in combination with other agents, primarily thiazide diuretics.

1.2. Clinical Background
Losartan is a synthetic oral angiotensin-II receptor (type AT\textsubscript{1}) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT\textsubscript{1} receptor 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 cell proliferation.

1.3. Indications
- Treatment of essential hypertension in adults and in children and adolescents 6 - 18 years of age.
- Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria $\geq 0.5$ g/day as part of an antihypertensive treatment
- Treatment of chronic heart failure in adult patients when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction $\leq 40\%$ and should be stabilised under the treatment of the chronic heart failure.
- Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

1.4. Posology and method of administration
Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).

Losartan potassium may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Hypertensive type II diabetic patients with proteinuria $\geq 0.5$ g/day
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on
blood pressure response from one month onwards after initiation of therapy. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

**Heart Failure**
The usual initial dose of losartan potassium in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily, 100 mg daily, up to a maximum dose of 150 mg once daily) as tolerated by the patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide should be added and/or the dose of losartan should be increased to 100 mg once daily based on blood pressure response.

**Special populations**

*Use in patients with intravascular volume depletion:*
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered.

*Use in patients with renal impairment and haemodialysis patients:*
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

*Use in patients with hepatic impairment:*
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.

**Paediatric population**

*6 months – less than 6 years*
The safety and efficacy of children aged 6 months to less than 6 years has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on posology can be made.

*6 years to 18 years*
For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. In exceptional cases the dose can be increased to a maximum of 50 mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in paediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.

It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m², as no data are available (see also section 4.4).

Losartan is also not recommended in children with hepatic impairment.
Use in Elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

2. Clinical Pharmacology

2.1. Pharmacokinetics
Losartan Potassium is a well known active substance and the pharmacokinetic characteristics have been studied in the past. The applicant has submitted a bioequivalence study in support of claims of essential similarity.

2.2. Bioequivalence
To support the application, the applicant has submitted two bioequivalence (BE) studies. Both BE studies are two-treatment, two period crossover studies. They follow the randomised open label comparison of Test and Reference products. Although Losartan exhibits linear pharmacokinetics, the 4 strengths sought have differences in composition and are not dose proportional, hence the applicant has provided one 25mg biostudy and another 100mg biostudy with respective biowaivers for 12.5 and 50mg strengths.

Biowaiver
As detailed above, all strengths are not dose proportional. The two lower strengths are dose proportional with similarity in composition (12.5 and 25mg) while the two higher strengths (50mg and 100mg) are proportional with similar compositions. In this situation, two biostudies would be appropriate.

The biowaiver is applicable to this sequence in order to fulfil the criteria for biowaiver as set out in the Bioequivalence note for Guidance.

Pharmacokinetic studies
The applicant has provided two biostudies;
A 25 mg biostudy-- relating to 12.5 and 25 mg strengths
A 100 mg biostudy------relating to 50 and 100mg strengths
Each study will be described in turn and results discussed at the end.

25 mg Biostudy:

Study title
Comparative bioequivalence study of 25 mg losartan after single dose administration (fasting conditions) of Blue 007 (Bluepharma) and Cozaar 25 mg (Merck Sharpe & Dohme Ltd., U.K.) in 46 healthy subjects.

Study design
This was a single-dose, randomised, open label, two-treatment, two-period, two-sequence cross-over study was conducted. The study was designed to determine the bioavailability of two formulations containing 25 mg losartan after single dose administration under fasting conditions in healthy subjects. The bioanalytical part of the study was carried out at Anapharm Europe.

Time schedule
Date of protocol: 31.07.2007
Study initiation date: 22.10.2007 (enrolment of first subject for screening)
Study completion date: 05.11.2007 (final examination of last subject)
Date of final report: 14.03.2008
Washout period 7 days

The applicant claims that the study complied with GCP and the Helsinki declarations.

**Sampling Schedule:**
After an overnight fasting of at least 12 hours at 8 a.m. (time 0) the subjects were administered 25 mg losartan in sitting position. 27 blood samples were drawn for pharmacokinetic analysis at the prescribed times (pre-dose (collected at least 15 min prior to dosing) and 10 min, 20 min, 30 min, 40 min, 50 min, 1 h, 1 h 10 min, 1 h 20 min, 1 h 30 min, 1 h 40 min, 1 h 50 min, 2 h, 2 h 15 min, 2 h 30 min, 2 h 45 min, 3 h, 3 h 30 min, 4 h, 4 h 30 min, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 hours after drug administration).

Both losartan and losartan carboxy acid (metabolite) were analysed as detailed before.

The design, the dose applied, the washout period and sampling sequence are considered adequate. The sampling period is of adequate duration to cover 3 times the anticipated half-life of losartan, the parent compound.

The study is stated to comply with GCP and is in accordance with Declaration of Helsinki.

**Test and reference products**

**Test formulation**
The test formulation was Blue 007, a film coated tablet of containing 25mg Losartan

**Reference formulation**
The reference formulation was Cozaar 25mg

**Population(s) studied**
The population studied were 46 healthy male and female caucasian subjects, aged 18-55 years with BMI of 19-28 were recruited.

**Protocol deviations;**
There were minor protocol deviations relating to time of sampling according to the report but no major protocol violations were noted.

**Analytical methods**
The bioanalysis was performed at the analytical facility of SFBC Anapharm, Europe located in Barcelona. A validated HPLC method using MS was employed to determine the plasma concentrations of Losartan and Losartan carboxy acid. Finasteride was used an internal control. Determination was conducted considering GLP-guideline. Process of validation and acceptance criteria are based on rules and guidelines of the FDA and the ICH Consensus Guideline. Losartan and losartan carboxy acid were analysed in EDTA K3 plasma using a method validated at Anapharm Europe. The method was revalidated before starting measurement of the samples. During the study quality control samples were analysed together with the samples in order to control accuracy and repeatability.

**Pharmacokinetic Variables**
Calculations of the pharmacokinetic parameters and the assessment of bioequivalence were carried out for losartan and losartan carboxy acid. The bioavailability was estimated using following parameters:
Primary parameters:
- AUC_t
- AUC_∞
- C_max

Additional parameters:
- $t_{max}$
- $t_{1/2}$
- Residual area; AUC_t(last) - ∞ calculated as a difference between AUC_∞ and AUC_t expressed as percentage value.

Statistical methods

The statistical analysis was performed by using SAS (SAS Software Version 9.1.3, Copyright © by SAS Institute Inc., Cary, NC, USA). Non-zero Log-transformed data were used for Analysis of Variance (ANOVA) for AUC_t, AUC_∞ and C_max. The primary pharmacokinetic parameters after logarithmic transformation were subjected to an analysis of variance (ANOVA), using a general linear model with the factors sequence, subjects nested within sequence, period and drug formulation. The test for normality of the residual distribution was performed on ln-transformed data from one of the study periods using the Wilk-Shapiro procedure. In case of significant deviations from the assumption of normal distribution the OLS ANOVA procedure was judged as invalid and data was analysed employing the non-parametric Wilcoxon-Mann-Whitney-tests procedure.

For assessment of bioequivalence 90%-confidence intervals for the formulation ratio in the parameters AUC_t, AUC_∞ and C_max of losartan and losartan carboxy acid were calculated using the ln-transformed data. Bioequivalence was accepted if the calculated 90%-confidence intervals are within 0.80 - 1.25 for AUC_t and 0.75 – 1.33 for C_max.

Results

Table 1. PK parameters for LOSARTAN (parent)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_0-t ng/ml·h</th>
<th>AUC_0-∞ ng/ml·h</th>
<th>C_max ng/ml</th>
<th>$t_{max}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arithmetic means</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>225.48 ± 74.825</td>
<td>233.49 ± 78.22</td>
<td>112.69 ± 54.297</td>
<td>0.95 ± 0.534</td>
</tr>
<tr>
<td>Reference</td>
<td>231.52 ± 82.441</td>
<td>239.14 ± 84.789</td>
<td>112.50 ± 65.176</td>
<td>1.21 ± 0.854</td>
</tr>
<tr>
<td><strong>Geometric means</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test*</td>
<td>213.39</td>
<td>221.00</td>
<td>100.31</td>
<td>0.83</td>
</tr>
<tr>
<td>Reference*</td>
<td>218.23</td>
<td>225.62</td>
<td>94.43</td>
<td>0.99</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td><strong>0.978</strong> (0.95 -- 1.01)</td>
<td><strong>0.980</strong> (0.95 -- 1.011)</td>
<td><strong>1.062</strong> (0.91 -- 1.227)</td>
<td></td>
</tr>
<tr>
<td>Intrasubject CV (%)</td>
<td>9.15%</td>
<td>8.75%</td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

*ln-transformed values

Table 2; PK parameters for Metabolite (Losartan carboxy acid)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_0-t ng/ml·h</th>
<th>AUC_0-∞ ng/ml·h</th>
<th>C_max ng/ml</th>
<th>$t_{max}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arithmetic means</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>865.80 ± 314.09</td>
<td>940.21 ± 316.07</td>
<td>86.62 ± 41.29</td>
<td>5.42 ± 2.12</td>
</tr>
<tr>
<td>Reference</td>
<td>855.78 ± 303.88</td>
<td>936.58 ± 307.33</td>
<td>84.73 ± 40.59</td>
<td>5.98 ± 2.06</td>
</tr>
</tbody>
</table>
No significant period effect was noted apparently and no sequence effect was noted either. The pre-dose samples for period two are claimed to be below the LOQ of the assay. Number of the subjects experienced $C_{max}$ at the first sampling time. The residual area was <20% for the overall group (mean values) and for all individuals independently.

There were fifteen adverse events observed in ten subjects. These were headache, rush and dizziness. All were classified as mild. Fourteen were classified as possible and one as probable/likely study drug related. In seven subjects eight events were observed with test medication and in seven subjects seven events were observed with reference medication.

All parameters fulfil the conventional acceptance criteria for bioequivalence in that all 90% CI are within 80.00-125.00%. Two subjects were withdrawn from the study voluntarily and this was for non medical reasons. Conclusion of study results is based on pharmacokinetic data evaluation and statistical analysis of 44 subjects.

100 mg Biostudy; LSA-P7-088

**Study title:**
Single dose cross over comparative bioavailability study of Losartan 100mg film coated tablets in fasted healthy male and female volunteers.

**Study design**

The design was essentially similar to the 25mg study described above. There were minor differences in inclusion criteria and other aspects. This was a single centre, randomised, laboratory blinded, two period, two treatment study. There was a washout period of 7 days between the two periods.

Blood sampling was carried out as follows after drug administration at the following times for each period; pre dose, and 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10, 12, 16, 24 and 36 hours post dose. Dosing in each period was at 8 Am on day 0 after a 10 hours fast and the subjects were confined to the testing facility for 24 hours.

The report claims that the study was conducted in accordance to GCP requirements and the declaration of Helsinki. The date of ethical approval of the study is unclear form the report but other aspects seem to be in order.

The design of the study follows the conventional phase-I study to establish bioequivalence and the inclusion /exclusion criteria, the washout period and the protocol are adequate. As Losartan has an active metabolite (carboxy acid) both parent and metabolite were assayed in the plasma.

**Test and reference products**

Losartan BLPHI 100mg film coated tablets has been compared to Cozaar® 100mg film coated tablets.
Population(s) studied

Overall 40 subjects were planned for inclusion into the study. There was on dropout and hence 39 were included in the study report. All were Caucasian healthy male and female subjects, who were non-smokers, aged between 18-45 years with a BMI of 19-30 kg/Sq.M. Female subjects were included only if pregnancy test was confirmed negative. All subjects needed to be HBsAg and HIV negative.

Analytical methods

The analytes included losartan and the metabolite, losartan carboxy acid. The method of analysis was HPLC with MS detection. Bioanalytical part of the study was carried out at Algorithme Pharma in Laval, Quebec. Finasteride was used an internal control. The range of assay was 5.00ng/ml to 1500ng/ml.

Pharmacokinetic Variables

Standard PK parameters were evaluated; AUC, AUC_{inf}, and C_{max} were primary parameters. The secondary parameters were, T_{max}, t_{1/2}, Kel, and residual area.

A noncompartmental approach with trapezoidal rule to estimate area under the curve were used.

Statistical methods

Statistical analysis was based on a parametric ANOVA model of the PK parameters; two sided 90% confidence interval of the ratio of geometric means for C_{max}, AUC, and AUC_{inf} based on log transformed data were used. T_{max} evaluation was based on non-parametric approach. The overall level of significance was at two sided 5% level.

For the ANOVA model, the following were used as fixed factors; Study group, treatment, period (nested within study group), sequence, study by sequence interaction and study by treatment interaction. Subject effect (nested within the study by sequence interaction) was the random factor.

Bioequivalence;

Bioequivalence was concluded if the 90% confidence intervals of GM ratio (test /Ref) was between the standard intervals of 80-125% for AUC, and AUC_{inf}.

For C_{max}, proposals for widening to 75-133% based on the in use CPMP note for guidance were pre-defined in the protocol. All results were within the 80-125 % limits.

Results

Table 1. PK parameters for LOSARTAN (parent)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arithmetic means</th>
<th>Geometric means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC_{0-t} ng/ml-h</td>
<td>AUC_{0-\infty} ng/ml-h</td>
</tr>
<tr>
<td>Test</td>
<td>757.26 ±283.48</td>
<td>781.49±288.64</td>
</tr>
<tr>
<td>Reference</td>
<td>741.11±268.03</td>
<td>763.02±268.34</td>
</tr>
<tr>
<td>Geometric means</td>
<td>705.69</td>
<td>728.94</td>
</tr>
<tr>
<td>Reference*</td>
<td>696.42</td>
<td>718.00</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>101.33 (95.21 - 107.85)</td>
<td>101.52 (95.62--107.78)</td>
</tr>
<tr>
<td>Intraserbect CV (%)</td>
<td>16.3</td>
<td>15.7</td>
</tr>
</tbody>
</table>

*In-transformed values
Table-2  PK parameters for Metabolite (Losartan carboxy acid)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; ng/ml·h</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; ng/ml·h</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; ng/ml</th>
<th>t&lt;sub&gt;max&lt;/sub&gt; h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arithmetic means</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>3903.13 ±1504.08</td>
<td>3962.91 ±1508.72</td>
<td>692.79 ± 309.97</td>
<td>3.14 ±1.06</td>
</tr>
<tr>
<td>Reference</td>
<td>3926.06 ± 417.83</td>
<td>3986.69±1418.83</td>
<td>681.98 ± 291.88</td>
<td>2.96 ±1.06</td>
</tr>
<tr>
<td>Geometric means</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test*</td>
<td>3754.12</td>
<td>3824.37</td>
<td>617.06</td>
<td></td>
</tr>
<tr>
<td>Reference*</td>
<td>3803.96</td>
<td>3884.41</td>
<td>632.44</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>98.69</td>
<td>98.45</td>
<td>97.57</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(94.73 -102.81)</td>
<td>( 94.65 -102.42)</td>
<td>(90.86 -- 104.77)</td>
<td></td>
</tr>
<tr>
<td>Intrasubject CV (%)</td>
<td>10.7</td>
<td>10.3</td>
<td>18.7</td>
<td></td>
</tr>
</tbody>
</table>

*ln-transformed values

No significant period effect was noted apparently and no sequence effect was noted either. The pre-dose samples for period two are claimed to be below the LOQ of the assay. No of the subjects experienced Cmax at the first sampling time. The residual area was <20% for the overall group (mean values) and for all individuals independently.

Twenty five of the 40 subjects experienced a total of 54 ADRs during the study. Twenty-eight (18 types) were reported after the Test product and 26 (15 types) were reported with the reference product. Three possibly drug related events (axillary mass, increase lymphocyte count and lymphadenopathy) were unexpected but not considered serious.

In both studies all parameters (C<sub>max</sub>, AUC<sub>t</sub> and AUC<sub>inf</sub>) fulfilled the criteria for bioequivalence as defined in the CPMP note for guidance, CPMP/EWP/QWP/1401/98. The two studies were conducted by different CROs and the study reports are a testament to the differences in approach.

Pharmacokinetic conclusion

Based on the submitted bioequivalence studies, LOSARTAN BLPHI tablets could be considered bioequivalent with COZAAR® tablets.

The results of study LSA-P7-088 with 100mg formulation can be extrapolated to the 50 mg tablet, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4. and, similarly, the results of the 25 mg study could be extrapolated to the 12.5 mg strength tablet

2.3. Pharmacodynamics
The pharmacodynamic characteristics of losartan potassium have been well-studied in the past. There would be no particular concerns for a generic medicinal product.

3. Clinical Efficacy
No new data have been submitted and none are required.

4. Clinical Safety
No new data have been submitted and none are required.

5. Expert Reports
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory.
6. Conclusion
The medical assessor recommended that Marketing Authorisation were granted for these products.

V. OVERALL CONCLUSION, BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Losartan Potassium 12.5 mg, 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.

NONCLINICAL
No new nonclinical data were submitted and none are required for applications of these type.

EFFICACY
No new or unexpected safety concerns arise from these applications.

The SmPCs and PIL are satisfactory and consistent with that of the reference products.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with losartan potassium is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

Losartan Potassium 12.5 mg Film-coated Tablets
Losartan Potassium 12.5, 25, 50, and 100 mg Film-coated Tablets

Losartan Potassium 25 mg Film-coated Tablets
Losartan Potassium 50 mg Film-coated Tablets
Losartan Potassium 100 mg Film-coated Tablets

INGREDIENTS
Each film-coated tablet contains Losartan Potassium 100 mg. Also contains Lactose.

DOSEAGE
For oral administration. Use as directed by your physician.

WARNING
KEEP OUT OF SIGHT AND REACH OF CHILDREN

Please affix dispensing label here

Please affix your own dispensing label here

K/R/Drug/KTK/25/169/04
STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

The following table lists a non-safety update to the Marketing Authorisations (PL 21880/0139-0142) for these products that has been approved by the MHRA since the products were first licensed. The table include an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/12/2017</td>
<td>Type IB</td>
<td>To update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3 and 6, of the Summary of Product Characteristic, SmPC, in line with the brand leader. Consequently, the Patient Information Leaflet has also been updated.</td>
<td>Approved on 21 February 2018</td>
</tr>
</tbody>
</table>
Annex 1

Our Reference: PL 21880/0139 – 0016
PL 21880/0140 – 0016
PL 21880/0141 – 0016
PL 21880/0142 – 0017

Product: Losartan potassium 12.5 mg film-coated tablets
Losartan potassium 25 mg film-coated tablets
Losartan potassium 50 mg film-coated tablets
Losartan potassium 100 mg film-coated tablets

Marketing Authorisation Holder: Medreich Plc

Active Ingredient(s): Losartan potassium.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard

Reason:
To update sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3 and 6, of the Summary of Product Characteristic, SmPC in line with the brand leader. Consequently, the Patient Information Leaflet has also been updated.

Supporting Evidence
A copy of the reference SmPC and PIL)
Revised SmPC fragments and updated PIL.

Evaluation
The proposed changes to the SmPC and PIL are satisfactory.

Conclusion
The proposed changes to the SmPC and PIL are considered acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision - Approved on 21 February 2018