Public Assessment Report

Decentralised Procedure

Losartan Potassium 25 mg film-coated tablets
Losartan Potassium 50 mg film-coated tablets
Losartan Potassium 100 mg film-coated tablets
(Losartan potassium)

Procedure No: UK/H/0899/001-003/DC

UK Licence No: PL 04569/1099-1101

Generics (UK) Limited
LAY SUMMARY

Losartan Potassium 25 mg film-coated tablets
Losartan Potassium 50 mg film-coated tablets
Losartan Potassium 100 mg film-coated tablets
(losartan potassium)

This is a summary of the Public Assessment Report (PAR) for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets (PL 04569/1099-1101, previously PL 17871/0009-0011; UK/H/0899/001-003/DC). It explains how the applications for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets.

For practical information about using Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Losartan Potassium’ in this report.

What is Losartan Potassium and what is it used for?
Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets are ‘generic medicines’. This means that Losartan Potassium is similar to ‘reference medicines’ already authorised in the UK called Cozaar 25 mg, 50 mg and 100 mg film-coated tablets (PL 00025/0036; PL 00025/0324, PL 00025/0416 Merck, Sharp & Dohme), which were first authorised in the UK in 1994.

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, medicines 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 you 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”).

How does Losartan Potassium work?
Losartan Potassium contains the active ingredient losartan (as losartan potassium), which 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 increase in blood pressure. Losartan prevents the binding of angiotensin-II to those receptors, causing 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.

How is Losartan Potassium used?
Losartan Potassium is available as film-coated tablets, in three strengths: 25 mg, 50 mg and 100 mg. The tablets should be swallowed with a glass of water. The tablets may be taken with or without food. The patient should always take Losartan Potassium exactly as advised by the doctor or pharmacist. The
patient should check with the doctor or pharmacist if not sure.

The patient’s doctor will decide on the appropriate dose of Losartan Potassium, depending on the patient’s condition and whether the patient is taking other medicines. It is important to continue taking Losartan Potassium for as long as the doctor prescribes it in order to maintain smooth control of the blood pressure.

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.

Losartan Potassium can only be obtained with a prescription. The patient should check with the doctor or pharmacist if he/she is not sure about what to do.

**What benefits of Losartan Potassium have been shown in studies?**

As Losartan Potassium 25mg, 50 mg and 100 mg film-coated tablets are generic medicines, studies in patients have been limited to tests to determine that Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets are bioequivalent to the reference medicines, Cozaar 25 mg, 50 mg and 100mg Tablets (Merck, Sharp & Dohme, UK), respectively. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder has provided data from the published literature on Losartan Potassium.

**What are the possible side effects of Losartan Potassium?**

Because Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets are generic medicines and are bioequivalent to the reference medicines Cozaar Tablets (Merck, Sharp & Dohme, UK), the benefits and possible side effects are taken as being the same as those of the reference medicines.

For the full list of all side effects reported with Losartan Potassium, see section 4 of the package leaflet.

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

**Why is Losartan Potassium approved?**

It was concluded that, in accordance with EU requirements, Losartan Potassium has been shown to have comparable quality and to be comparable to Cozaar Tablets (Merck, Sharp & Dohme; UK). Therefore, the MHRA decided that, as for Cozaar Tablets (Merck, Sharp & Dohme; UK), the benefits outweigh the identified risks and recommended that Losartan Potassium can be approved for use.

**What measures are being taken to ensure the safe and effective use of Losartan Potassium?**

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Losartan Potassium, 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 Losartan Potassium**

The Netherlands and the UK agreed to grant a Marketing Authorisation for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets on 23 April 2007. Marketing Authorisations for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets (PL 17871/0009-0011) were granted in the UK to Jenson Pharmaceutical Services Limited on 06 June 2007.
Subsequent to a Change of Ownership procedure, the Marketing Authorisations for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets were granted to Generics (UK) Limited (PL 04569/1099-1101) on 23 October 2009.

The full PAR for Losartan Potassium follows this summary.

For more information about treatment with Losartan Potassium, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2015.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I Introduction Page 6
II Quality aspects Page 7
III Non-clinical aspects Page 15
IV Clinical aspects Page 15
V User consultation Page 16
VI Overall conclusion, benefit/risk assessment and recommendation Page 16

Annex 1 - Table of content of the PAR update for MRP and DCP Page 17
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Netherlands and the UK considered that the applications for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets (PL 17871/0009-0011; UK/H/0899/001-003/DC), in the treatment of hypertension, reduction of stroke in those with left ventricular hypertrophy and renal protection, could be approved.

The applicant has provided reasons by stating that the study results (Life study) supported the wording only for reduction of stroke; these are acceptable. The RMS is in agreement with this.

Hypertension is a chronic disorder and a major risk factor for cardiovascular morbidity and mortality. The treatment of hypertension is complex with various classes of drugs available with variable benefits. These include diuretics, calcium channel blockers, beta-blockers, ACE inhibitors and angiotensin receptor blockers. In these applications, authorisation is sought for generic forms of Losartan, an angiotensin receptor blocker for the following indications:

- Hypertension
- Reduction of risk of stroke in those hypertensives with left ventricular hypertrophy
- Renal protection in type 2 diabetic patients with nephropathy (macroalbuminuria).

Losartan is the prototype angiotensin receptor blocker that was first authorised in several European Union Member States in 1994 for the treatment of hypertension. Since then several other indications have been added based on large clinical trial data that include the indications stated above.

These applications were submitted, under Article 10(1) of Directive 2001/83/EC, as amended, as generic applications, using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and the Netherlands as Concerned Member State (CMS). The current formulations under discussion, Losartan Potassium film coated Tablets (25 mg, 50 mg, and 100 mg) are generic preparations manufactured by Liconsa SA. These are immediate release formulations to be marketed in the UK and the Netherlands by Jenson Pharmaceuticals Services Limited. The applications are considered to be generic medicinal products of Cozaar Tablets (25 mg, 50 mg and 100 mg, respectively; Merck, Sharp and Dohme), which were first authorised in the UK in 1994.

The dossier is of acceptable quality. The Quality and non-clinical expert reports are of adequate standard and acceptable. The applicant has provided the required bioavailability/bioequivalence study.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The UK and the Netherlands considered that the applications could be approved at the end of procedure (Day 150) on 23 April 2007. After a subsequent national phase, licences were granted to Jenson Laboratories Services Limited in the UK on 06 June 2007.

Subsequent to Change of Ownership procedures, the Marketing Authorisations for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets were granted to Generics (UK) Limited (PL 04569/1099-1101) on 23 October 2009.
II QUALITY ASPECTS

II.1 Introduction

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.

Each Losartan Potassium 25 mg, 50 mg or 100 mg film-coated tablet contain 25 mg, 50 mg or 100 mg of losartan potassium, respectively. The tablets are round, white film-coated tablets.

The products also contain the pharmaceutical excipients in the tablet core and film-coat, namely lactose monohydrate, pregelatinised maize starch, microcrystalline cellulose, magnesium stearate, hydroxypropylcellulose, hypromellose and titanium dioxide (E171). Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in polvinylidene chloride/polyethylene/aluminium (PVDC/PE/aluminium) blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with European Union legislation regarding contact with food.

II.2 DRUG SUBSTANCE – LOSARTAN POTASSIUM

rINN: Losartan Potassium

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

Chemical Abstracts Service (CAS) number: [124750-99-8]

Structure:

Molecular formula: \( \text{C}_{22}\text{H}_{22}\text{ClKN}_{6}\text{O} \)
Molecular weight: 461.0
Appearance: White to off-white crystalline powder
Solubility Freely soluble in water and in methanol, slightly soluble in acetonitrile.

Losartan potassium is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting material 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.
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 analyses 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 supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the pharmaceutical development programme was to produce Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets that could be considered as generic products to the originator products Cozaar 25 mg, 50 mg and 100 mg film-coated tablets (Merck, Sharp & Dohme).

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

Dissolution and impurity profiles
Dissolution and impurity profiles for the drug products were found to be similar to that for the reference products.

Excipients
All the excipients comply with their respective European Pharmacopoeia monographs. 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
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Control of Finished Product
The finished product specifications are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 all working standards used.
Stability of the Product
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 30 months with the special storage conditions of ‘Store in the original package.’ has been set. This is acceptable.

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 products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The proposed products have been shown to be generic products of the reference products and have met the requirements with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisations should be granted for these applications.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, 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 SmPCs and PIL are available on the MHRA website. The current labelling is presented below:
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of losartan potassium 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 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.
The clinical pharmacology of losartan potassium is well-known. With the exception of data from the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or are required for these applications.

IV.2 Pharmacokinetics
The applicant has provided the requisite biostudy in support of these applications. A single biostudy comparing 100 mg strengths of Losartan tablets, test and reference, has been included in the dossier. Acceptance criteria are satisfactory and the results support the claim for bioequivalence between test and reference products.

The applicant has fulfilled the essential criteria for biowaiver for the two lower strengths as per section 5.4 of the CHMP guidance note (CPMP/EWP/QWP/1401/98).

IV.3 Pharmacodynamics
The pharmacodynamics properties of losartan potassium are well established. No new data were submitted and none were required for these applications.

IV.4 Clinical Efficacy
The clinical efficacy of losartan potassium is well-known. No new efficacy data are presented or are required for this type of application.

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 this type of application. No new or unexpected safety issues arose during the bioequivalence study.
IV.6 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets.

V. USER CONSULTATION

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of losartan potassium 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 this type of application.

Bioequivalence has been demonstrated between the applicant’s 100 mg strength product and the reference product Cozaar 100 mg film-coated tablets (Merck, Sharp & Dohme, Spain), under fasting conditions. The applicant has fulfilled the essential criteria for biowaiver for the two lower strengths (25 mg and 50 mg) as per section 5.4 of the CHMP guidance note (CPMP/EWP/QWP/1401/98).

SAFETY

No new data are submitted and none are required for applications of this type. The safety of losartan has been well established for use in the indications sought and sufficient published literature has been submitted in support of this. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE

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

BENEFIT/RISK ASSESSMENT

Losartan Potassium 25mg, 50 mg and 100 mg film-coated tablets are generic products with losartan potassium as the active ingredient. The documentation with regard to quality, non-clinical and clinical is satisfactory. Bioequivalence with the originator has been established for the 100mg strength and biowaiver criteria fulfilled for the 25 mg and 50 mg strengths.

RECOMMENDATION

The grant of Marketing Authorisations is recommended.
## Annex 1 - Table of content of the PAR update for MRP and DCP

### Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

The following table lists non-safety updates to the Marketing Authorisations that are of clinical significance for these products. This may not be a complete list of the post authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To update the SmPC, PIL and labelling in accordance with Article 30 Referral EMEA/CHMP/494721/2008.</td>
<td>UK/H/0899/001, -003/II/002</td>
<td>SmPC, PIL and labelling</td>
<td>01/05/2009</td>
<td>18/08/2009</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>To introduce HDPE bottles with silica desiccant gel contained in a polypropylene lid in pack sizes of 100 tablets.</td>
<td>UK/H/0899/001-003/IB/006</td>
<td>SmPC, PIL and labelling</td>
<td>27/08/2010</td>
<td>16/-9/2010</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>To register an additional pack size of 250 film tablets, for the bottle presentation. Section 6.5 has been updated</td>
<td>UK/H/0899/001-003/IA/008</td>
<td>SmPC, PIL and labelling</td>
<td>01/10/2010</td>
<td>01/11/2010</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>To update sections 1, 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3, 6.1, 6.2, 6.3, 6.4, 6.5 and 6.6 of the SmPC in line with the Brand Leader (Cozaar) and current Quality Review of Documents (QRD) template. As a consequence, the PIL has been updated.</td>
<td>UK/H/0899/001-003/IB/022</td>
<td>The SmPC and PIL</td>
<td>19/05/2015</td>
<td>25/07/2015</td>
<td>Approval</td>
<td>Y(Annex 1.1)</td>
</tr>
</tbody>
</table>
ANNEX 1.1

Our Reference: PL 04569/1099 –0021; PL 04569/1100-0023; PL 04569/1101-0023
Products: Losartan Potassium 25 mg, 50 mg and 100 mg film-coated tablets
Marketing Authorisation Holder: Generics (UK) Limited
Active Ingredient(s): Losartan potassium.

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/0899/001-003/IB/022

Reason:
To update sections 1, 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3, 6.1, 6.2, 6.3, 6.4, 6.5 and 6.6 of the Summary of Product Characteristics (SmPC) in line with the brand leader (Cozaar) and current Quality Review of Documents (QRD) template. As a consequence, the Patient Information Leaflet (PIL) has been updated.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 163693 and covers the following submissions PL 04569/1101 - 0023, PL 04569/1100 - 0023.

Supporting Evidence
Revised SmPC fragments (sections) and updated leaflet have been provided.

Evaluation
The updated sections of the SmPC and leaflet are acceptable.

Conclusion
The updated sections of the SmPC, the updated labelling and the leaflet are satisfactory 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 16 July 2015