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LAY SUMMARY

Losartan Potassium 25mg, 50mg, & 100mg Film-coated Tablets
(losartan potassium)

This is a summary of the public assessment report (PAR) for Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets. This summary explains how Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets.

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

What are Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets and what are they used for?
Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets are ‘generic medicines’. This means that Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets are similar to ‘reference medicines’ already authorised in the European Union (EU) called Cozaar 25mg, 50mg and 100 Film-coated Tablets.

Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets are used:

- in the treatment of high blood pressure (hypertension) in adults and in children and adolescents aged 6-18 years old
- to protect the kidneys, by blocking the harmful effects of angiotensin in hypertensive type 2 diabetic patients with laboratory evidence of impaired renal function and proteinuria (a condition in which urine contains an abnormal amount of protein). Losartan slows the worsening of kidney damage and reduces the need for dialysis or a kidney transplant.

How is Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets used?
This is a prescription only medicine. Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets should be swallowed with a glass of water. The usual starting dose is 50mg of one losartan potassium tablet, once a day. The maximal blood pressure lowering effect should be reached 3-6 weeks after beginning treatment. In some patients the dose may be later increased to 100mg.

The appropriate dose is decided by the doctor, who will take into consideration additional factors such as other medication that is being administered and the general condition of the individual.

How do Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets work?
Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets contain the active ingredient losartan potassium. Losartan potassium belongs to a group of medicines known as angiotensin-II antagonists. Angiotensin-II is a substance produced in the body which causes blood vessels to tighten. This causes blood pressure to rise. Losartan potassium blocks the effect of angiotensin II on blood vessels which causes blood vessels to relax, which in turn lowers the blood pressure.

How have Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets been studied?
Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets are generic medicines; studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Cozaar 25mg, 50mg and 100 Film-coated Tablets.

Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the benefits and risks of Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets?
Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets are generic medicines and they are bioequivalent to the reference medicine. Therefore, the benefits and risks are taken as being the same as the reference medicine.

Why are Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to Cozaar 25mg, 50mg and 100 Film-coated Tablets. Therefore, the view was that, as for Cozaar 25mg, 50mg and 100 Film-coated Tablets, the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets?
Safety information has been included in the Summary of Product Characteristics and the package leaflets for Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets
Marketing Authorisations were granted in the UK to Jubilant Pharmaceuticals nv (PL 19156/0058-0060) on 02 December 2009.

A change of ownership procedure was granted on 27 January 2010 to change the authorisation holder to Waymade Healthcare Plc (trading as Sovereign Medical) PL 06464/2740-2742.

This summary was last updated in April 2014.

The full initial PAR published prior to the change of authorisation procedure for Losartan Potassium 25mg, 50mg, and 100mg Film-coated Tablets (PL 19156/0058-0060 granted; 02 December 2009) follows this summary. Updates to the PAR since 02 December 2009 can be found in Annex 1, this is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.
Losartan Potassium 25mg, 50mg, & 100mg film-coated Tablets
PL 19156/0058-0060
(losartan potassium)

SCIENTIFIC DISCUSSION

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Pharmaceutical assessment ......................... Page 7
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Clinical assessment .................................. Page 11
Overall conclusion and risk benefit assessment  Page 15
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Jubilant Pharmaceuticals NV Marketing Authorisations (licences) for the medicinal products Losartan Potassium 25mg film-coated Tablets (PL 19156/0058), Losartan Potassium 50mg film-coated Tablets (PL 19156/0059), and Losartan Potassium 100mg film-coated Tablets (PL 19156/0060) on 2nd December 2009. These are prescription-only medicines.

These are abridged, national applications for Losartan Potassium 25mg, 50mg and 100mg film-coated Tablets. These are three strengths of Losartan potassium, submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal versions of the reference products, Cozaar 25mg, 50mg, and 100mg film-coated tablets respectively (PL 00025/0336, 0324, and 0416 resp), authorised to Merck, Sharp & Dohme Limited on 15th December 1994 (0336 and 0324) and on 28th November 2001 (0416). The reference products have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

Losartan Potassium film-coated Tablets are indicated in:

- Treatment of essential hypertension
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5g/day as part of an antihypertensive treatment
- Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of chronic heart failure.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (See section 5.1 of SmPCs)

Losartan is a synthetic oral, specific 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.

Losartan selectively blocks the AT₁ receptor. 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 its synthesis.

During losartan administration, removal of the angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to increases in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockage. After discontinuation of Losartan, PRA and angiotensin II values fell within three days to the base line values.

Both losartan and its principal active metabolite have a far greater affinity for the AT₁ receptor than the AT₂ receptor. The active metabolite is 10 to 40 times more active than losartan on a weight for weight basis.
These applications for Losartan Potassium 25mg, 50mg and 100mg film-coated Tablets were submitted at the same time and are supported by the bioequivalence study presented comparing the applicant’s 50mg product with the clinical reference product Cozaar 50mg film-coated tablets, Merck, Sharp & Dohme Limited. Consequently, all sections of the Scientific Discussion refer to all three products.

As the test products, Losartan Potassium 25mg, 50mg and 100mg film-coated Tablets, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength product were extrapolated to the 25mg and 100mg strength tablets.

The pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The marketing authorisation holder has provided adequate justification for not submitting a Risk Management Plan (RMP) and Environmental Risk Assessment (ERA).
ACTIVE SUBSTANCE

Losartan potassium

Nomenclature:

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) 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[2’-(1H-tetrazol-5-yl)[1,1’-biphenyl]-4-y1]methyl]-, monopotassium salt

Structure:

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

Molecular formula: \( \text{C}_{22}\text{H}_{22}\text{ClK}_{6}\text{O} \)

Molecular weight: 461.00 g/mol

CAS No: 124750-99-8

Physical form: White to off-white powder

Solubility: Freely soluble in water, sparingly soluble in isopropyl alcohol, slightly soluble in acetonitrile

The active substance, losartan potassium, is the subject of a European Pharmacopeia (Ph. Eur.) 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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been 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 and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in double polythene bags followed by a triple laminated bag and HDPE drum. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 1 year.
DRUG PRODUCT

Description and Composition

Each white to off-white, oval shaped, film-coated tablet contains 25mg, 50mg, or 100mg of losartan potassium. Please refer to the respective SmPCs for details of markings on the individual tablets.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose (E460), pregelatinised starch, lactose monohydrate, and magnesium stearate (E572) making up the tablet cores; and hypromellose (E464), hydroxypropylcellulose (E463), and titanium dioxide (E171) constituting the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Appropriate TSE/BSE documentation was provided for lactose monohydrate.

There were no novel excipients used and no overages.

Dissolution profiles

Comparative dissolution data were provided for each strength of the proposed generic losartan potassium tablets against the reference tablet formulations. The dissolution profiles were found to be similar and were satisfactory.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation was performed on the first two pilot scale batches of each of the strengths.

Finished product specification

Finished product specifications are provided for release and end of shelf life and are acceptable; the specifications provide an assurance of the quality and consistency of the finished products. 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 for the two pilot scale batches of each of the strengths and comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in PVC (polyvinylchloride) / PVDC (polyvinylidene chloride) / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The tablets are packaged in pack sizes of 10, 28, 30, 50, 56, 90, 98 and 100 tablets. The MA Holder has stated that not all pack sizes may be marketed.
Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. These medicinal products do not require any special storage conditions.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Losartan Potassium 50mg film-coated Tablets, to the reference product, Cozaar 50mg film-coated tablets (Merck, Sharp & Dohme Limited).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

**Quality Overall Summary**

A satisfactory QOS is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

**Product Information**

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

**Conclusion**

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Losartan Potassium 50mg film-coated Tablets is a generic medicinal product of Cozaar 50mg film-coated tablets appears justified.

As the test products, Losartan Potassium 25mg, 50mg and 100mg film-coated Tablets, meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength product were extrapolated to the 25mg and 100mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It was, therefore, recommended that Marketing Authorisations be granted.
**PRECLINICAL ASSESSMENT**

These abridged applications are for Losartan Potassium 25mg, 50mg and 100mg film-coated Tablets and were submitted under Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical overview has been written by a suitably qualified expert and is satisfactory. An appropriate CV for the expert has been supplied.
INDICATIONS
Losartan Potassium 25mg, 50mg and 100mg film-coated Tablets are indicated in:

- Treatment of essential hypertension
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5g/day as part of an antihypertensive treatment
- Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of chronic heart failure.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (See section 5.1)

The indications are consistent with those of the innovator products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Full details concerning the posology are provided in the SmPCs.

The posology is consistent with that of the reference products and is satisfactory.

TOXICOLOGY
No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY
Pharmacodynamics
No new data have been submitted and none are required for these types of application.

Losartan is a synthetic oral, specific angiotensin-II receptor (type AT₁) antagonist (ATC Code: C09CA01). 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.

Losartan selectively blocks the AT₁ receptor. 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 its synthesis.

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During losartan administration, removal of the angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to increases in angiotensin II in
plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockage. After discontinuation of Losartan, PRA and angiotensin II values fell within three days to the base line values.

Both losartan and its principal active metabolite have a far greater affinity for the AT$_1$ receptor than the AT$_2$ receptor. The active metabolite is 10 to 40 times more active than losartan on a weight for weight basis.

Pharmacokinetics

No new data have been submitted. The pharmacokinetics of losartan potassium are well described in the product SmPCs.

**Pharmacokinetics - Bioequivalence study**

The applicant presented a single bioequivalence study comparing the test product, Losartan Potassium 50mg film-coated Tablets, to the reference product, Cozaar 50mg film-coated tablets (Merck, Sharp & Dohme Limited). Satisfactory Certificates of Analysis for the test and reference products were provided. The use of the 50mg strength tablet for the bioequivalence study has been adequately justified.

This was a conventional; randomised, single-dose, open-label, two-treatment, two-sequence, two-period, two-way crossover study designed to assess the bioavailability of the test product versus the reference product under fasting conditions, conducted in 90 (86 plus 4 reserves) healthy adult human (male and female) subjects. The study was of an appropriate design and was conducted to principles of Good Clinical Practice.

A single dose of the investigational products was administered orally with 240 ml of water to each subject in each period, after an overnight fast. Treatment periods 1 and 2 were separated by a satisfactory washout period of 7 days. Blood samples were taken pre-dose (0.0) and at specified time points up to 48.0 hours after administration of test or reference product. Plasma samples were analysed for losartan potassium and its active metabolite, losartan carboxy acid, using an appropriate, validated HPLC / MS / MS method.

The primary pharmacokinetic parameters for the studies were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.
Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

**Biostudy outcome and results:**

88 of the 90 volunteers completed the study. 86 were used in the statistical analysis. One volunteer did not report for period II and one was discontinued on medical grounds during period II. There were no deaths or serious adverse events.

The results for the main pharmacokinetic parameters are reported as follows.

Pharmacokinetic results for losartan and losartan carboxy acid for a randomised, two-treatment, two-period, single dose crossover study. n=86 healthy subjects, dosed fasted. Wash-out period: 7 days

<table>
<thead>
<tr>
<th>Variable</th>
<th>Geometric means</th>
<th>Point Estimate (Test/reference) (%)</th>
<th>90 % C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generic 50 mg</td>
<td>Cozaar 50 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tablets (test)</td>
<td>tablets (reference)</td>
<td></td>
</tr>
<tr>
<td>Losartan (n=86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>198.533</td>
<td>214.946</td>
<td>92.36</td>
</tr>
<tr>
<td>$AUC_{(0-\infty)}$ (ngh/ml)</td>
<td>455.415</td>
<td>471.947</td>
<td>96.50</td>
</tr>
</tbody>
</table>
The 90% confidence intervals of the ratios for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ were within the accepted limits of 80 – 125%, as specified in the CPMP/EWP/QWP/1401/98 Note for Guidance and as pre-specified in the study protocol.

**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasted conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Losartan Potassium 25mg and 100mg film-coated Tablets. As Losartan Potassium 25mg, 50mg and 100mg film-coated Tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 50mg strength were extrapolated to the 25mg and 100mg strength tablets.

**EFFICACY**

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of losartan potassium is well-established from its extensive use in clinical practice.

**SAFETY**

No new data are submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of losartan potassium is well-known.

**EXPERT REPORT**

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

**PRODUCT INFORMATION:**

**Summary of Product Characteristics (SmPCs)**

The text of the SmPCs is in line with the harmonized text of the innovator product and is satisfactory.

**Patient Information Leaflet**

The final PIL is in line with the approved SmPCs and is satisfactory.

**Labelling**

The labelling is satisfactory.
CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and bioequivalence of the 50mg strength test and reference products was shown with 90% Confidence Intervals within general acceptance limits.

The conditions, as detailed in CPMP/EWP/QWP/1401/98, for a single bioequivalence study to cover multiple strengths of a product have been met, so the results and conclusions of the bioequivalence study were extrapolated to the 25mg and 100mg strength tablets. It is therefore concluded that the 25mg and 100mg strength formulations are bioequivalent to their corresponding marketed brand formulations, despite bioequivalence not being assessed explicitly.

Sufficient clinical information has been submitted to support these applications. When used as indicated, losartan potassium has a favourable benefit-to-risk ratio. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

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

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Losartan Potassium 50mg film-coated Tablets, and the reference product Cozaar 50mg film-coated tablets (PL 00025/0324, Merck, Sharp & Dohme Limited).

As the test products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence studies on the 50mg strength were extrapolated to the 25mg and 100mg strength tablets, and omission of further bioequivalence studies can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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 testing shows that patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s products and their respective reference products are interchangeable. Extensive clinical experience with losartan potassium is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.
Losartan Potassium 25mg, 50mg, & 100mg film-coated Tablets
PL 19156/0058-0060

(losartan potassium)

STEPS TAKEN FOR ASSESSMENT

1  The MHRA received the marketing authorisation applications on 9\textsuperscript{th} October 2008

2  Following standard checks and communication with the applicant the MHRA considered the applications valid on 14\textsuperscript{th} October 2008

3  Following assessment of the applications the MHRA requested further information relating to the quality and clinical dossiers on 23\textsuperscript{rd} February 2009

4  The applicant responded to the MHRA’s request, providing further information for the quality and clinical sections on 27\textsuperscript{th} May 2009

5  Following assessment of the responses the MHRA requested further information relating to the quality sections on 5\textsuperscript{th} October 2009

6  The applicant responded to the MHRA’s requests, providing further information for the quality sections on 2\textsuperscript{nd} November 2009

7  The applications were determined on 2\textsuperscript{nd} December 2009
**Losartan Potassium 25mg, 50mg, & 100mg film-coated Tablets**  
**PL 06464/2740-2742**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>04 March 2010</td>
<td>Type 1B</td>
<td>To update section 4.1 (Therapeutic indications) of the SmPC and the PIL to delete indications for treatment of chronic heart failure, stroke, and impaired renal function as they are still patented, with consequential updates to sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects) &amp; 5.1 (Pharmacodynamic properties).</td>
<td>23 March 2010</td>
</tr>
<tr>
<td>03 October 2012</td>
<td>Type 1B</td>
<td>To update sections 4.1, 4.2, 4.5, 4.8, 4.9 and 5.1 of the SmPC in order to bring it in line with the originator product; Cozaar 100mg tablets. As a consequence the PIL has been updated</td>
<td>Granted 03 April 2014</td>
</tr>
</tbody>
</table>
Annex 1

Reference:
PL 06464/2740-0011
PL 06464/2741-0011
PL 06464/2742-0011

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

2) The following amendments should be introduced in the PIL in line with the innovator:

- The indication should be in line with the SPC: “Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age."

Response
This has been amended as requested. The PIL now reads:
- “to treat high blood pressure (hypertension) in adults and in children and adolescents aged 6 to 18 years old;”

Please see:
m1-3-2-PIL-losartan-proposed-highlighted.pdf
m1-3-2-PIL-losartan-proposed-clean.pdf

- Section 3 should be in line with the indication:
  Use in children and adolescents (6 to 18 years old)

Response
This has been amended as requested. Please see:
m1-3-2-PIL-losartan-proposed-highlighted.pdf
m1-3-2-PIL-losartan-proposed-clean.pdf

- Section 4: As per the annotated QRD template, please amend as shown.
  Common (affects less than 1 in 10, but more than 1 in 100 patients) (may affect up to 1 in 10 people).
  Uncommon (affects less than 1 in 100, but more than 1 in 1,000 patients) (may affect up to 1 in 100 people).
  Rare (affects less than 1 in 1,000, but more than 1 in 10,000 patients) (may affect up to 1 in 1,000 people).

Response
This has been amended as requested. Please see:
m1-3-2-PIL-losartan-proposed-highlighted.pdf
m1-3-2-PIL-losartan-proposed-clean.pdf
Summary of Product Characteristics and Patient Information Leaflet

The current approved UK versions of the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PILs) for these products are available on the MHRA website.
LABELLING

Losartan Potassium 25mg film-coated tablets