Lisinopril 2.5 mg Tablets
Lisinopril 5 mg Tablets
Lisinopril 10 mg Tablets
Lisinopril 20 mg Tablets
(PL 11311/0511-4)

UKPAR

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LAY SUMMARY
Lisinopril 2.5 mg Tablets
Lisinopril 5 mg Tablets
Lisinopril 10 mg Tablets
Lisinopril 20 mg Tablets
(lisinopril dihydrate)

This is a summary of the public assessment report (PAR) for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0511-4). It explains how Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg 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 Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets.

For practical information about using Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets and what are they used for?
These products contain the active substance lisinopril dihydrate. They are used in the treatment or prevention of high blood pressure (hypertension), heart failure, kidney disease resulting from high blood pressure and diabetes, and in patients recovering from a heart attack (myocardial infarction).

These products are identical to Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7), which are already authorised in the UK to the same Marketing Authorisation Holder (Tillomed Laboratories Limited).

How are Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets used?
These products can only be obtained with a prescription.

How do Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets work?
Lisinopril is one of a group of medicines known as ACE (Angiotensin–Converting Enzyme) Inhibitors. These work by expanding the blood vessels, making it easier for the heart to pump blood around the body.

How have Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets been studied?
These applications are identical to the previously granted licences for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7, Tillomed Laboratories Limited), which, in turn, cross-referred to the licences for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 10880/0012-5, Hexal AG). The company referred to data provided for the grant of the licences for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7) as a basis for the grant of these identical licences for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0511-4).

What are the benefits and risks of Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets?
As Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0511-4) are considered identical to Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL
their benefits and risks are taken as being the same as for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7).

**Why are Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets approved?**

No new or unexpected safety concerns arose from these duplicate applications of Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7). Therefore, the view was that, as for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7), the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets?**

Safety information has been included in the Summary of Product Characteristics and the package leaflet for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets**

Marketing authorisations were granted for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets on 04 November 2013. For more information about treatment with Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets, read the package leaflet or contact your doctor or pharmacist.

The full PAR for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets follows this summary.

This summary was last updated in 11-2013.
LISINOPRIL 2.5 MG TABLETS
LISINOPRIL 5 MG TABLETS
LISINOPRIL 10 MG TABLETS
LISINOPRIL 20 MG TABLETS
(PL 11311/0511-4)

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations to Tillomed Laboratories Limited for the medicinal products Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0511-4) on 04 November 2013.

These products are prescription-only medicines (legal status POM). They are used for the treatment of hypertension; the treatment of symptomatic heart failure; the short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction; and the treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy.

These were submitted as abridged simple applications according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7), which were granted Marketing Authorisations to Tillomed Laboratories Limited on 03 August 2009. The reference products were granted licences via abridged simple applications, cross referring to Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 10880/0012-5), which were granted Marketing Authorisations to Hexal AG on 22 October 2001. These licences (PL 10880/0012-5) have since been cancelled in the UK.

These products contain the active substance lisinopril dihydrate, which is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II, which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

Whilst the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low renin hypertension. ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 11311/0511-4
PROPRIETARY NAME: Lisinopril 2.5 mg Tablets
Lisinopril 5 mg Tablets
Lisinopril 10 mg Tablets
Lisinopril 20 mg Tablets
ACTIVE(S): lisinopril dihydrate
COMPANY NAME: Tillomed Laboratories Limited
E.C. ARTICLE: Article 10c
LEGAL STATUS: POM

1. INTRODUCTION
These are simple, piggyback applications for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets, submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed MA holder is Tillomed Laboratories Limited, 3 Howard Road, Eaton Socon, St Neots, Cambridgeshire, PE19 8ET, United Kingdom.

The applications cross-refer to Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7), which were originally granted to Tillomed Laboratories Limited on 03 August 2009.

The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed names of the products are Lisinopril 2.5 mg Tablets, Lisinopril 5 mg Tablets, Lisinopril 10 mg Tablets and Lisinopril 20 mg Tablets. The products have been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each 2.5 mg tablet contains 2.72 mg lisinopril dihydrate, which is equivalent to 2.5 mg lisinopril.
Each 5 mg tablet contains 5.44 mg lisinopril dihydrate, which is equivalent to 5 mg lisinopril.
Each 10 mg tablet contains 10.89 mg lisinopril dihydrate, which is equivalent to 10 mg lisinopril.
Each 20 mg tablet contains 21.78 mg lisinopril dihydrate, which is equivalent to 20 mg lisinopril.

The finished product is packaged in polyvinylchloride/aluminium blisters packed in cardboard boxes, in the following pack sizes:
Lisinopril 2.5 mg Tablets – 14, 28, 30, 50 and 100 tablets
Lisinopril 5 mg Tablets – 10, 14, 28, 30, 30x1, 50, 56, 60, 98 and 100 tablets
Lisinopril 10 mg Tablets – 10, 14, 28, 30, 50, 98 and 100 tablets
Lisinopril 20 mg Tablets – 10, 14, 28, 30, 50, 56, 98, 100 and 100x1 tablets
Not all pack sizes are to be marketed. However, the Marketing Authorisation Holder has committed to submitting mock-ups to the regulatory authorities for approval before marketing any pack size.

The proposed shelf-life (4 years) and storage conditions (no special storage conditions) are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Tillomed Laboratories Limited, 3 Howard Road, Eaton Socon, St Neots, Cambridgeshire, PE19 8ET, United Kingdom.

The QP responsible for pharmacovigilance is stated and their CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
No materials of animal or human origin are included in these products. This is consistent with the cross-reference products.

2.11 Bioequivalence
No bioequivalence data are required to support these informed consent applications, as the proposed products are manufactured to the same formulae, utilising the same processes as the reference products Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7).

3. EXPERT REPORTS
The applicant has included expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the
quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. **PRODUCT NAME & APPEARANCE**
See 2.1 for details of the proposed product names. The appearance of the products is identical to the cross-reference products.

5. **SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)**
The proposed SmPCs are consistent with the details registered for the cross-reference products.

6. **PATIENT INFORMATION LEAFLET (PIL)/LABEL**

   PIL
   The patient information leaflet has been prepared in line with the details registered for the cross-reference products.

   Carton and blister
   The proposed artwork is comparable with the artwork registered for the cross reference products and complies with statutory requirements. The applicant has included sufficient space for a standard UK pharmacy dispensing label.

7. **CONCLUSIONS**
The data submitted with the applications is acceptable. From a quality perspective, Marketing Authorisations should be granted.

**NON-CLINICAL ASSESSMENT**

No new non-clinical data have been supplied with these applications and none are required for applications of this type.

An Environmental Risk Assessment (ERA) has not been provided. As these products are intended for substitution with products that are already marketed, no increase in environmental burden is anticipated.

The grant of Marketing Authorisations is recommended.

**CLINICAL ASSESSMENT**

No new clinical data have been supplied with these applications and none are required for applications of this type.

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.
Suitable justification has been provided for not submitting a risk management plan for these products.

The grant of Marketing Authorisations is recommended.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data provided for these applications are consistent with that previously assessed for the cross-reference products and as such have been judged to be satisfactory. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted applications for Lisinopril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (PL 11311/0394-7), which were originally granted to Tillomed Laboratories Limited on 03 August 2009. No new clinical pharmacology/efficacy data have been submitted with these applications and none are required for applications of this type.

SAFETY
No new safety data have been submitted with these applications and none are required for applications of this type.

No new or unexpected safety concerns have arisen from these applications.

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

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with lisinopril dihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Lisinopril 2.5, 5, 10 & 20 mg Tablets
(PL 11311/0511-4)

**Steps Taken for Assessment**

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<td>1</td>
<td>The MHRA received the marketing authorisation applications on 31 May 2012.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant, the MHRA considered the applications valid on 29 June 2012.</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information relating to the dossiers on 21 August 2012.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 22 October 2012.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 04 November 2013.</td>
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LISINOPRIL 2.5 MG TABLETS
LISINOPRIL 5 MG TABLETS
LISINOPRIL 10 MG TABLETS
LISINOPRIL 20 MG TABLETS
(PL 11311/0511-4)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Application type</th>
<th>Scope</th>
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Summary of Product Characteristics and Patient Information Leaflet
In accordance with Directive 2010/84/EU, the current approved UK versions of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for these products are available on the MHRA website.
Labelling

Lisinopril 2.5mg Tablets
- Each tablet contains 2.72mg of lisinopril dihydrate, equivalent to 2.5mg of lisinopril.
- For oral use. Read the enclosed leaflet before use. Keep out of the reach and sight of children. (POM)

Product Licence Holder:
Tillomed Laboratories Ltd.,
3 Howard Road, Eaton Socon, St Neots,
Cambs PE19 8ET, UK

PL 11311/0511

Lisinopril 2.5mg Tablets
- Each tablet contains 2.72mg of lisinopril dihydrate, equivalent to 2.5mg of lisinopril.

Attach dispensing label here