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LAY SUMMARY

Ramipril 1.25 mg Capsules
Ramipril 2.5 mg Capsules
Ramipril 5 mg Capsules
Ramipril 10 mg Capsules

This is a summary of the Public Assessment Report (PAR) for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules (PL 25298/0037-40). It explains how Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules 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 Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules.

For practical information about using Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

The products may be referred to as Ramipril Capsules in this report.

What are Ramipril Capsules and what are used for?
These medicines are the same as Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077), which are already authorised. The company (Morningside Healthcare Ltd, UK) that makes Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules, (PL 20117/0074-0077) has agreed that its scientific data can be used as a basis for the grant of identical licence for Ramipril Capsules (PL 25298/0037-40) (informed consent).

Ramipril Capsules can be used:
- to treat high blood pressure (hypertension)
- to reduce the risk of having a heart attack or stroke
- to reduce the risk or delay the worsening of kidney problems (whether or not the patient has diabetes).
- to treat the heart when it cannot pump enough blood to the rest of the body (heart failure)
- as treatment following a heart attack (myocardial infarction) complicated with heart failure.

How do Ramipril Capsules work?
The active ingredient, ramipril, belongs to a group of medicines called ACE inhibitors (Angiotensin Converting Enzyme Inhibitors).

Ramipril Capsules work by:
- decreasing the body’s production of substances that could raise the blood pressure
- making the blood vessels relax and widen making it easier for the heart to pump blood around the body.

How are Ramipril Capsules used?
These medicines should always be taken exactly as instructed by the doctor. If unsure, the patient should check with the doctor or pharmacist.

Taking this medicine
- Ramipril Capsules should be taken by mouth at the same time of day, each day
- The capsules should be swallowed with liquid
- The capsules should not be chewed or crushed.
Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Ramipril Capsules can only be obtained with a prescription.

**What benefits of Ramipril Capsules have been shown in studies?**
The applications for Ramipril Capsules (PL 25298/0037-40) are considered to be identical to the previously authorised licences for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077), with the same benefits and risks. So, no new studies have been provided for Ramipril Capsules (PL 25298/0037-40). However, reference is made to the studies for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules, (PL 20117/0074-0077).

**What are the possible side effects from Ramipril Capsules?**
Like all medicines, Ramipril Capsules can cause side effects, although not everybody gets them.

As Ramipril Capsules are considered to be identical to Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077), their side effects are taken as being the same as that for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077).

For a full list of all the side effects reported with Ramipril Capsules, see section 4 of the package leaflet available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

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

**Why are Ramipril Capsules approved?**
No new or unexpected safety concerns arose from these applications. The MHRA, therefore, considered that the benefits of Ramipril Capsules outweigh their risks; and the grant of Marketing Authorisations was recommended.

**What measures are being taken to ensure the safe and effective use of Ramipril Capsules?**
A Risk Management Plan has been developed to ensure that Ramipril Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Ramipril Capsules, 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 as well.

**Other information about Ramipril Capsules**
Marketing Authorisations were granted in the UK on 05 November 2014.

The full PAR for Ramipril Capsules follows this summary.

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

This summary was last updated in January 2015.
Ramipril 1.25 mg Capsules
Ramipril 2.5 mg Capsules
Ramipril 5 mg Capsules
Ramipril 10 mg Capsules

PL 25298/0037-40

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Brown and Burk UK Limited Marketing Authorisations for the medicinal products Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules (PL 25298/0037-40) on 05 November 2014. The products are prescription-only medicines (POM) indicated for:

- Treatment of hypertension.
- Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:
  - Manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
  - Diabetes with at least one cardiovascular risk factor (see section 5.1 of the Summary of Product Characteristics (SmPC)).
- Treatment of renal disease
  - Incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria,
  - Manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor (see section 5.1 of the SmPC),
  - Manifest glomerular non diabetic nephropathy as defined by macroproteinuria $\geq 3$ g/day (see section 5.1 of the SmPC).
- Treatment of symptomatic heart failure.
- Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started $> 48$ hours following acute myocardial infarction.

The applications were submitted as abridged applications according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules, (PL 20117/0074-0077, Morningside Healthcare Limited, UK) which were granted on 01 April 2008 following a number of Change of ownership procedures of the original licences Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 18843/0010-13; Endwell limited, Ireland) which were authorised in the UK on 08 January 2004.

Ramipril Capsules contain the active ingredient ramipril. Ramipril is a prodrug, which after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active ACE inhibitor, ramiprilat. Administration of Ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance.

No new data were submitted nor were necessary to be submitted for these applications, as the data are identical to those of the previously granted cross-reference products.
1. INTRODUCTION
These are abridged applications for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg (PL 25298/0037-40) submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077; Morningside Healthcare Ltd, UK), which were granted Marketing Authorisations in the UK on 01 April 2008. The applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1. Name
The proposed names of the products are Ramipril 1.25mg, 2.5mg, 5mg and 10mg capsules. The products have been named in line with current requirements.

2.2. Strength, pharmaceutical form, route of administration, container and pack sizes
Each capsule contains 1.25 mg, 2.5 mg, 5 mg or 10 mg of ramipril.

The products are packaged in Aluminium/aluminium (Al/Al) blisters, in pack sizes of 7, 21, 28, 30, 50 and 100 capsules.

The products are packed with the Patient Information Leaflet into cardboard outer cartons.

Not all pack sizes may be marketed.

The proposed shelf lives are 18 months (1.25 mg and 24 months (2.5 mg, 5 mg and 10 mg), with the storage conditions ‘Do not store above 25°C. Store in the original packaging.’

The packaging, proposed shelf-life and storage conditions are consistent with the details registered for the respective cross-reference products.

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

2.4. Marketing Authorisation Holder/Contact Persons/Company
Brown & Burk UK Limited, 5 Marryat Close, Hounslow West, Middlesex, TW4 5DQ, United Kingdom

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

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 compositions are 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 respective cross-reference products and the maximum batch sizes are stated.

2.8. Finished product/shelf-life specification
The proposed finished product specifications are consistent with the details registered for the respective 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
With the exception of gelatin, none of the excipients contain materials of animal or human origin.

The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that it is manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE). This is consistent with the cross-reference products.

2.11. Bioequivalence
No bioequivalence data are required to support these simple abridged applications because the proposed products are manufactured to the same formula and utilise the same processes as the reference products Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077; Morningside Healthcare Ltd, UK).

3. EXPERT REPORT
The applicant cross-references to the data for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077; Morningside Healthcare Ltd, UK) to which these applications are claimed to be identical. This is acceptable.

4. PRODUCT NAME AND APPEARANCE
See Section 2.1 for details of the proposed product names. The appearance of each product is identical to the respective cross-reference product.

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

6. PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The Patient Information Leaflet has been prepared in line with the details registered for the cross-reference products.

Morningside Healthcare Limited has previously submitted results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077). The results indicate that the 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.
User-testing of the PIL for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg (PL 25298/0037-40) has been accepted based on the bridging report provided by the applicant making reference to the successful user-testing of the PIL for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077) as the 'parent PIL’.

Carton and label
The proposed artwork is consistent with the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation, the applicant has also included the names of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSION
The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

An acceptable Risk Management Plan (RMP) has been submitted. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

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 licences for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 20117/0074-0077; Morningside Healthcare Ltd, UK).

SAFETY
No new safety data were supplied or required for these applications. Ramipril has a well-established safety profile. No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE
The SmPCs and PIL are satisfactory, and consistent with those for the cross-reference products. The labelling complies with statutory requirements and is satisfactory.

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

1. The MHRA received the Marketing Authorisation applications on 21 October 2013.
2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 06 November 2013.
3. Following assessment of the applications the MHRA requested further information relating to the dossiers on 22 January 2014, 23 May 2014 and 29 July 2014.
4. The applicant responded to the MHRA’s request, providing further information on the 13 March 2014, 20 June 2014 and 01 September 2014.
5. The applications were granted on 05 November 2014.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
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will be Embossed online
UKPAR Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules

PL 25298/0037-40

Embossing area for batch details
LOT XXXXXXX EXP MM/YY
will be Embossed online