RAMIPRIL 1.25MG, 2.5MG, 5MG AND 10MG TABLETS
PL 33410/0033-36

UKPAR

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RAMIPRIL 1.25MG, 2.5MG, 5MG AND 10MG TABLETS
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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Marketing Authorisations (licences) for Ramipril Tablets on 9th August 2010. The tablets are available in a number of different strengths in order that the most appropriate dose can be prescribed. These are 1.25mg, 2.5mg, 5mg and 10mg of ramipril.

These medicines are only available on a prescription from your doctor. They are used to treat the following conditions:

- high blood pressure (hypertension),
- reduce the risk of heart attack or stroke,
- reduce the risk or delay worsening kidney problems,
- heart failure and as treatment following a heart attack complicated by heart failure.

The marketing authorisation holder is Apsla Limited.

Ramipril Tablets work by widening the blood vessels and making it easier for the heart to pump blood through them and around the body. This helps reduce blood pressure and helps the heart work better if the heart muscle is damaged.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Ramipril 1.25mg, 2.5mg, 5mg and 10mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
RAMIPRIL 1.25MG, 2.5MG, 5MG AND 10MG TABLETS
PL 33410/0033-36

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Ramipril 1.25mg, 2.5mg, 5mg and 10mg Tablets (PL 33410/0033-36) to Apsla Limited on 9th August 2010. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The applications refer to the reference products, Tritace 1.25mg, 2.5mg, 5mg and 10mg Tablets (PL 04425/0356-9), currently authorised to Sanofi-Aventis. Tritace was first approved in the UK in November 1989. The reference products have been authorised in the EEA for over 10 years.

The product contains the active ingredient ramipril, which is a pro-drug and is converted to the active metabolite ramiprilat by liver enzymes.

No new non-clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of the originator products that have been licensed for over 10 years.

A single-dose, fasting bioequivalence study was submitted to support the applications. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of the reference products that have been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Ramipril 1.25mg, 2.5mg, 5mg and 10mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Ramipril
INN: Ramipril


CAS No: 87333-19-5

Structure

![Chemical Structure of Ramipril](image)

Molecular mass: 416.51
Molecular formula: C_{23}H_{32}N_{2}O_{5}

General Properties

Description: A white or almost white, crystalline powder. Freely soluble in methanol, sparingly soluble in water.

Polymorphism: There is no evidence of ramipril polymorphism in the literature.

Manufacture

Synthesis of the drug substance from the designated starting materials 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.
Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

**DRUG PRODUCT**

**Other ingredients**
The drug products, each containing 1.25mg, 2.5mg, 5mg and 10mg of the active ingredient ramipril are presented as capsule shaped, biconvex, uncoated tablets with the strength of the tablet debossed on one side and a central breakline on the other side. Full descriptions of the colours and markings of the individual tablets may be found by referring to the Summary of Product Characteristics/patient information leaflet.

Other ingredients consist of pharmaceutical excipients, namely hypromellose, pregelatinised starch, maize starch, microcrystalline cellulose, colloidal anhydrous silica and sodium stearyl fumarate and are present in each strength of tablets in the proposed product range. In addition to the excipients mentioned above the 2.5mg strength (yellow) tablets contains yellow iron oxide (E172) and the 5mg strength (pink) tablets contain red iron oxide (E172). Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their relevant European Pharmacopoeia (Ph. Eur) monographs with the exception of yellow iron oxide and red iron oxide both of which comply with suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process of the proposed product.

**Pharmaceutical Development**
Details of the pharmaceutical development of the medicinal products have been provided and are satisfactory. The aim of the pharmaceutical development was to formulate an acceptable, stable and bioequivalent tablet dosage form of Ramipril Tablets, comparable to the reference products Tritace® Tablets (Sanofi Aventis).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference products.

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

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted.
Finished Product Specification
The finished product specifications are provided for both release and shelf-life and 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. Satisfactory batch analysis data are provided and accepted. Certificates of Analysis have been provided for any reference standards used.

Container Closure System
The finished product is licensed for marketing in blister strips composed of polyvinylchloride (PVC)/aluminium foil. The blisters are packaged with the patient information leaflet into outer cardboard cartons. The tablets are packaged in pack sizes of 28.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. 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 3 years has been set, which is satisfactory. Storage conditions are instructions are ‘Store below 30°C’, “Keep the blister in the outer carton in order to protect from light”.

Bioequivalence Study
A bioequivalence study was presented comparing the test product, Ramipril 5mg Tablets, to the reference product, Tritace® 5mg Tablets (Sanofi-Aventis, UK).

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

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SPCs, PILs and labelling are pharmaceutically acceptable.

MAA form
The MAA forms are pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

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

These applications were submitted as national, abridged, standard applications, according to Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of ramipril well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The curriculum vitae of the expert has been provided.

Asuitable justification has been provided for the non-submission of an environmental risk assessment.
CLINICAL ASSESSMENT

Pharmacokinetics
In support of these applications the marketing authorisation holder has compared the pharmacokinetic profiles of Ramipril 5mg Tablets (test) and Tritace® 5 mg Tablets- Sanofi Aventis (reference). Satisfactory Certificates of Analysis for the test and reference products have been provided. The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP).

To demonstrate bioequivalence the prodrug should be measured. Levels of the active metabolite may also be measured to provide further confirmation of bioequivalence. Conventional bioequivalence acceptance criteria apply to this drug substance (80-125% for $C_{\text{max}}$ and AUC).

Study design
This was a single centre, randomized, single-dose, open-label, 2-way crossover bioequivalence, performed under fasting conditions. The treatment phases were separated by a washout period of 28 days.

A total of 44 healthy volunteers were enrolled of which 39 completed the study. A satisfactory explanation and justification of drop-outs have been provided.

Randomisation
Volunteers were randomised to one of the possible sequences and the randomisation was balanced for sequence.

Administration of study medication
A single 5 mg dose of test and reference products was administered with 240 ml of water. Subjects were dosed after an overnight fast.

Washout period
The washout period was 28 days which is considered adequate although it is noted that subject 37 had more than 5 % of $C_{\text{max}}$ for ramiprilat during pre-dose for period II.

Less than or equal to 5 % $C_{\text{max}}$ was the concentration stated in the protocol as being acceptable at period II pre-dosing without subject adjustment. This is in-line with FDA and draft EU guidance and so can be accepted.

Sampling
Samples were taken pre-dose and over 288 hours which was sufficient for adequate estimation of AUC for both ramipril and its active metabolite.
Blood samples were drawn prior to drug administration and up to 288 hours post-dose in each period. Dosing intervals are also considered suitable for the determination of \( C_{\text{max}} \) (expected \( T_{\text{max}} \) for ramipril is 1 hour and 3-4 hours for its active metabolite). This was supported by the concentration-time curves for individual volunteers.

**Bio-analytical methods and validation**

Ramipril and ramiprilat were analysed from human plasma using a LC-MS/MS method following solid phase extraction.

In-process validation was accomplished using calibration curves and QC samples. The data are satisfactory.

Pre-study validation reports have also been provided. Method specificity, linearity, precision and accuracy and sample stability have been investigated, including determination of the limit of quantitation for ramipril and ramiprilat. Perindopril and perindoprilat were used as the internal standard. Data indicate that the method is suitable for the determination of both analytes.

**Statistical plan**

An adequate statistical plan was provided and the planned statistical methods were conventional. Log-transformed data for \( \text{AUC}_{(0-t)} \), \( \text{AUC}_{(0-inf)} \), and \( C_{\text{max}} \) were analysed by ANOVA. \( T_{\text{max}} \) was analysed using the Wilcoxon Signed-Rank test.

Calculated pharmacokinetic parameters are summarized in the following tables.

<table>
<thead>
<tr>
<th>Table 1 Pharmacokinetic Parameters of ramipril (upper panel) and ramiprilat (lower panel);</th>
</tr>
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<tbody>
<tr>
<td><strong>Ramipril Parameters</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>( N )</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
</tr>
<tr>
<td>( \text{AUC}_{0-4} ) (hr-ng/ml)</td>
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<tr>
<td>( \text{AUC}_{0-\infty} ) (hr-ng/ml)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Perindoprilat Parameters</strong></th>
<th>Geometric mean</th>
<th>(%)/R</th>
<th>90% Confidence Interval for ln-transformed data</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N )</td>
<td>39</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>5.44</td>
<td>5.12</td>
<td>105.75</td>
<td>97.01-115.29</td>
</tr>
<tr>
<td>( \text{AUC}_{0-4} ) (hr-ng/ml)</td>
<td>201.52</td>
<td>199.91</td>
<td>100.34</td>
<td>97.00-103.79</td>
</tr>
<tr>
<td>( **\text{AUC}_{0-\infty} ) (hr-ng/ml)</td>
<td>401.89</td>
<td>449.22</td>
<td>89.46</td>
<td>84.08-95.19</td>
</tr>
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</table>

**N=38 (excluding subject number 38)**

90% geometric confidence intervals of the ratio of least-squares means of the test to reference product of ln-transformed \( \text{AUC}_{0-t} \) and \( \text{AUC}_{0-inf} \) and \( C_{\text{max}} \) were included within 80% to 125%.

**GCP certification**

The applicant states that the study was performed in accordance to the current version of the Principles of Declaration of Helsinki and in compliance to the current ICH GCP.
Essential Similarity
Comparative dissolution and impurity profiles of the test and reference products from the UK have been provided and can be considered essentially similar. Furthermore, bioequivalence has been demonstrated using a pilot-scale batch of Ramipril 5 mg tablets.

Conclusion on Bioequivalence
The results of the bioequivalence study show that the test product and reference products are bioequivalent, after administration of a single dose under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $AUC_{0-1}$ and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in-line with current CHMP guidelines.

A satisfactory justification has been provided for a bio-waiver for Ramipril 1.25mg, 2.5mg and 10mg Tablets. As Ramipril 1.25mg, 2.5mg, 5mg and 10mg 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 5mg strength can be extrapolated to the 1.25mg, 2.5mg and 10mg strength tablets.

No new pharmacokinetics data have been submitted other than the bioequivalence study and none is required.

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
No new safety data have been submitted or required for this generic application. As ramipril is a well-known product with an acceptable adverse event profile, this is satisfactory.

Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form
The MAA form is medically satisfactory.

Conclusion
There are no objections to the approval of Ramipril 1.25mg, 2.5mg, 5mg and 10mg Tablets from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Ramipril 1.25mg, 2.5mg, 5mg and 10mg 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 5mg strength tablet and the reference product Tritace® 5 mg Tablets (Sanofi Aventis). As the 1.25mg, 2.5mg and 10mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study with the 5mg tablet strength can be extrapolated to the 1.25mg, 2.5mg and 10mg strengths.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPC and PIL are acceptable, and consistent with those for the reference products. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s ramipril 1.25mg, 2.5mg, 5mg and 10mg Tablets and the reference products Tritace® 1.25mg, 2.5mg, 5mg and 10mg Tablets (Sanofi-Aventis), are interchangeable. Extensive clinical experience with ramipril is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.

The SPCs, PIL and labelling are satisfactory and consistent with those for the innovator products.
### STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 18&lt;sup&gt;th&lt;/sup&gt; September 2008.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 23&lt;sup&gt;rd&lt;/sup&gt; September 2008.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 6&lt;sup&gt;th&lt;/sup&gt; February 2009, and 23&lt;sup&gt;rd&lt;/sup&gt; November 2009.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 7&lt;sup&gt;th&lt;/sup&gt; August 2009 and 18&lt;sup&gt;th&lt;/sup&gt; February 2010.</td>
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<tr>
<td>5</td>
<td>The application was determined on 9&lt;sup&gt;th&lt;/sup&gt; August 2010.</td>
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RAMIPRIL 1.25MG, 2.5MG, 5MG AND 10MG TABLETS
PL 33410/0033-36

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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RAMIPRIL 1.25MG, 2.5MG, 5MG AND 10MG TABLETS
PL 33410/0033-36

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Ramipril 1.25mg, 2.5mg, 5mg and 10mg Tablets (PL 33410/0033-36) is as follows- Differences are highlighted:

1 NAME OF THE MEDICINAL PRODUCT
Ramipril 1.25mg Tablets.
Ramipril 2.5mg Tablets.
Ramipril 5mg Tablets.
Ramipril 10mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1.25 / 2.5 / 5 / 10mg ramipril.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablets.

1.25mg: White, capsule shaped, biconvex, uncoated tablets debossed with 1.25 on one side and central breakline on other side.
2.5mg: Yellow, capsule shaped, biconvex, uncoated tablets debossed with 2.5 on one side and central breakline on other side.
5mg: Pink, capsule shaped, biconvex, uncoated tablets debossed with 5 on one side and central breakline on other side.
10mg: White, capsule shaped, biconvex, uncoated tablets debossed with 10 on one side and central breakline on other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

• Treatment of hypertension.

• Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:
  o manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
  o diabetes with at least one cardiovascular risk factor (see section 5.1).

• Treatment of renal disease:
  o Incipient glomerular diabetic nephropathy as defined by the presence of microalbuminuria,
  o Manifest glomerular diabetic nephropathy as defined by macroproteinuria in patients with at least one cardiovascular risk factor (see section 5.1),
  o Manifest glomerular non diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day (see section 5.1).

• 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.

4.2 Posology and method of administration

Oral use.

It is recommended that Ramipril is taken each day at the same time of the day. Ramipril can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2). Ramipril has to be swallowed with liquid. It must not be chewed or crushed.

**Adults**

**Diuretic-Treated patients**

Hypotension may occur following initiation of therapy with Ramipril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.

If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Ramipril (see section 4.4).

In hypertensive patients in whom the diuretic is not discontinued, therapy with Ramipril should be initiated with a 1.25 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Ramipril should be adjusted according to blood pressure target.

**Hypertension**

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control. Ramipril may be used in monotherapy or in combination with other classes of antihypertensive medicinal products.

**Starting dose**

Ramipril should be started gradually with an initial recommended dose of 2.5 mg daily. Patients with a strongly activated renin-angiotensin-aldosterone system may experience an excessive drop in blood pressure following the initial dose. A starting dose of 1.25 mg is recommended in such patients and the initiation of treatment should take place under medical supervision (see section 4.4).

**Titration and maintenance dose**

The dose can be doubled at interval of two to four weeks to progressively achieve target blood pressure; the maximum permitted dose of Ramipril is 10 mg daily. Usually the dose is administered once daily.

**Cardiovascular prevention**

**Starting dose**

The recommended initial dose is 2.5 mg of Ramipril once daily.

**Titration and maintenance dose**

Depending on the patient’s tolerability to the active substance, the dose should be gradually increased. It is recommended to double the dose after one or two weeks of treatment and - after another two to three weeks - to increase it up to the target maintenance dose of 10 mg Ramipril once daily.

See also posology on diuretic treated patients above.

**Treatment of renal disease**

**In patients with diabetes and microalbuminuria:**

**Starting dose:**
The recommended initial dose is 1.25 mg of Ramipril once daily.

**Titration and maintenance dose**
Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the once daily dose to 2.5 mg after two weeks and then to 5 mg after a further two weeks is recommended.

**In patients with diabetes and at least one cardiovascular risk**

**Starting dose:**
The recommended initial dose is 2.5 mg of Ramipril once daily.

**Titration and maintenance dose**
Depending on the patient's tolerability to the active substance, the dose is subsequently increased. Doubling the daily dose to 5 mg Ramipril after one or two weeks and then to 10 mg Ramipril after a further two or three weeks is recommended. The target daily dose is 10 mg.

**In patients with non-diabetic nephropathy as defined by macroproteinuria ≥ 3 g/day.**

**Starting dose:**
The recommended initial dose is 1.25 mg of Ramipril once daily.

**Symptomatic heart failure**

**Starting dose**
In patients stabilized on diuretic therapy, the recommended initial dose is 1.25 mg daily.

**Titration and maintenance dose**
Ramipril should be titrated by doubling the dose every one to two weeks up to a maximum daily dose of 10 mg. Two administrations per day are preferable.

**Secondary prevention after acute myocardial infarction and with heart failure**

**Starting dose**
After 48 hours, following myocardial infarction in a clinically and haemodynamically stable patient, the starting dose is 2.5 mg twice daily for three days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day the treatment should be withdrawn.

See also posology on diuretic treated patients above.

**Titration and maintenance dose**
The daily dose is subsequently increased by doubling the dose at intervals of one to three days up to the target maintenance dose of 5 mg twice daily. The maintenance dose is divided in 2 administrations per day where possible. If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn. Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be taken to treat these patients, it is recommended that therapy be started at 1.25 mg once daily and that particular caution be exercised in any dose increase.

**Special populations**

**Patients with renal impairment**
Daily dose in patients with renal impairment should be based on creatinine clearance (see section 5.2):
- if creatinine clearance is ≥ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 10 mg;
• if creatinine clearance is between 30-60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 5 mg;
• if creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg;
• in haemodialysed hypertensive patients: ramipril is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Patients with hepatic impairment (see section 5.2)
In patients with hepatic impairment, treatment with Ramipril must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg Ramipril.

Elderly
Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients. A reduced initial dose of 1.25 mg ramipril should be considered.

Paediatric population
Ramipril is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to the active substance, to any of the excipients or any other ACE (Angiotensin Converting Enzyme) inhibitors (see section 6.1)
• History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
• Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
• Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
• 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6)
• Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.

4.4 Special warnings and precautions for use
Warnings:
Special populations
Pregnancy: ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

- Patients at particular risk of hypotension

Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:
- patients with severe hypertension
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)
- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension. Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

- Transient or persistent heart failure post MI

- Patients at risk of cardiac or cerebral ischemia in case of acute hypotension
The initial phase of treatment requires special medical supervision.
  - Elderly patients
    See section 4.2.

Surgery
It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Monitoring of renal function
Renal function should be assessed before and during treatment and dosage adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment (see section 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after a renal transplant.

Angioedema
Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).
In case of angioedema, Ramipril must be discontinued. Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms. Intestinal angioedema has been reported in patients treated with ACE inhibitors including Ramipril (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).

Anaphylactic reactions during desensitization
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of Ramipril should be considered prior to desensitization.

Hyperkalaemia
Hyperkalaemia has been observed in some patients treated with ACE inhibitors including Ramipril. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, as well as thrombocytopenia and anaemia, have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopaenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

Ethnic differences
ACE inhibitors cause higher rate of angioedema in black patients than in non black patients. As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people than in non black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.
Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

4.5 Interaction with other medicinal products and other forms of interaction
Contra-indicated combinations
Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Precautions for use
Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim, tacrolimus, ciclosporin): Hyperkalaemia may occur, therefore close monitoring of serum potassium is required.

Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics)

Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of Ramipril: Blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count: Increased likelihood of haematological reactions (see section 4.4).

Lithium salts: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.

Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

Non-steroidal anti-inflammatory drugs and acetylsalicylic acid: Reduction of the antihypertensive effect of Ramipril is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

4.6 Pregnancy and lactation
Ramipril is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. ACE inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns
whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

Because insufficient information is available regarding the use of ramipril during breastfeeding (see section 5.2), ramipril is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines
Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient’s ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery). This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects
The safety profile of ramipril includes persistent dry cough and reactions due to hypotension. Serious adverse reactions include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.

Adverse reactions frequency is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Eosinophilia</td>
<td>White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased</td>
<td></td>
<td>Bone marrow failure, pancytopenia, haemolytic anaemia</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Vertigo, paraesthesia, ageusia, dysgeusia,</td>
<td>Tremor, balance disorder</td>
<td>Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td>------------------------------------------</td>
<td>--------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disturbance including blurred vision</td>
<td>Conjunctivitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Hearing impaired, tinnitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Non-productive tickling cough, bronchitis, sinusitis, dyspnoea</td>
<td>Bronchospasm including asthma aggravated, nasal congestion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting</td>
<td>Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth</td>
<td>Glossitis</td>
<td>Aphtous stomatitis</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash in particular maculo-papular</td>
<td>Angioedema; very exceptionally, the airway obstruction resulting from</td>
<td>Exfoliative dermatitis, urticaria, onycholysis,</td>
<td>Photosensitivity reaction</td>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis</td>
</tr>
</tbody>
</table>
angioedema may have a fatal outcome; pruritus, hyperhidrosis
psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia

| Musculoskeletal and connective tissue disorders | Muscle spasms, myalgia | Arthralgia |
| Metabolism and nutrition disorders | Blood potassium increased | Anorexia, decreased appetite, |
| Vascular disorders | Hypotension, orthostatic blood pressure decreased, syncope | Flushing |
| General disorders and administration site conditions | Chest pain, fatigue | Pyrexia |
| Immune system disorders | Hepatic enzymes and/or bilirubin conjugated increased, | Jaundice cholestatic, hepatocellular damage |
| Hepatobiliary disorders | Transient erectile impotence, libido decreased |
| Reproductive system and breast disorders | |
| Psychiatric disorders | Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence | Confusional state |

4.9 Overdose
Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure. The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE Inhibitors, plain, ATC code C09AA05.

Mechanism of action

Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Pharmacodynamic effects

Antihypertensive properties:
Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.

The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.

Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Heart failure:
In addition to conventional therapy with diuretics and optional cardiac glycosides, ramipril has been shown to be effective in patients with functional classes II-IV of the New-York Heart Association. The drug had beneficial effects on cardiac haemodynamics (decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index). It also reduced neuroendocrine activation.

Clinical efficacy and safety

Cardiovascular prevention/Nephroprotection:

A preventive placebo-controlled study (the HOPE-study), was carried out in which ramipril was added to standard therapy in more than 9,200 patients. Patients with increased risk of cardiovascular disease following either atherothrombotic cardiovascular disease (history of coronary heart disease, stroke or peripheral vascular disease) or diabetes mellitus with at least one additional risk factor (documented microalbuminuria, hypertension, elevated total cholesterol level, low high-density lipoprotein cholesterol level or cigarette smoking) were included in the study.

The study showed that ramipril statistically significantly decreases the incidence of myocardial infarction, death from cardiovascular causes and stroke, alone and combined (primary combined events).

The HOPE study: Main results

<table>
<thead>
<tr>
<th></th>
<th>Ramipril (%)</th>
<th>Placebo (%)</th>
<th>Relative Risk (95% confidence interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>n=4,645</td>
<td>N=4,652</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary combined events</td>
<td>14.0</td>
<td>17.8</td>
<td>0.78 (0.70-0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial</td>
<td>9.9</td>
<td>12.3</td>
<td>0.80 (0.70-0.90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### The MICRO-HOPE study

A predefined substudy from HOPE, investigated the effect of the addition of ramipril 10 mg to the current medical regimen versus placebo in 3,577 patients at least ≥ 55 years old (with no upper limit of age), with a majority of type 2 diabetes (and at least another CV risk factor), normotensive or hypertensive.

The primary analysis showed that 117 (6.5 %) participants on ramipril and 149 (8.4 %) on placebo developed overt nephropathy, which corresponds to a RRR 24 %; 95 % CI [3-40], p = 0.027.

The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study aimed at assessing the effect of treatment with ramipril on the rate of decline of glomerular function rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion > 1 and < 3 g/24 h) or severe proteinuria (≥ 3 g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

The main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in ramipril group) showed that the mean rate of GFR decline per month was lower with ramipril than with placebo; -0.54 (0.66) vs. -0.88 (1.03) ml/min/month, p = 0.038. The intergroup difference was thus 0.34 [0.03-0.65] per month, and around 4 ml/min/year; 23.1 % of the patients in the ramipril group reached the combined secondary endpoint of doubling of baseline serum creatinine concentration and/or end-stage renal disease (ESRD) (need for dialysis or renal transplantation) vs. 45.5 % in the placebo group (p = 0.02).

### Secondary prevention after acute myocardial infarction

The AIRE study included more than 2,000 patients with transient/persistent clinical signs of heart failure after documented myocardial infarction. The ramipril treatment was started 3 to 10 days after the acute myocardial infarction. The study showed that after an average follow-up time of 15 months the mortality in ramipril-treated patients was 16.9 % and in the placebo treated patients was 22.6 %. This means an absolute mortality reduction of 5.7 % and a relative risk reduction of 27 % (95 % CI [11-40 %]).

### 5.2 Pharmacokinetic properties

**Pharmacokinetics and Metabolism**

**Absorption**

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract: peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg ramipril is 45 %.

Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

**Distribution**

The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

**Metabolism**

---

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Placebo</th>
<th>Ramipril</th>
<th>Ratio</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>6.1</td>
<td>8.1</td>
<td>0.74</td>
<td>0.64-0.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.4</td>
<td>4.9</td>
<td>0.68</td>
<td>0.56-0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>10.4</td>
<td>12.2</td>
<td>0.84</td>
<td>0.75-0.95</td>
<td>0.005</td>
</tr>
<tr>
<td>Need for Revascularisation</td>
<td>16.0</td>
<td>18.3</td>
<td>0.85</td>
<td>0.77-0.94</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalisation for unstable angina</td>
<td>12.1</td>
<td>12.3</td>
<td>0.98</td>
<td>0.87-1.10</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>3.2</td>
<td>3.5</td>
<td>0.88</td>
<td>0.70-1.10</td>
<td>0.25</td>
</tr>
<tr>
<td>Complications related to diabetes</td>
<td>6.4</td>
<td>7.6</td>
<td>0.84</td>
<td>0.72-0.98</td>
<td>0.03</td>
</tr>
</tbody>
</table>

---
Ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.

**Elimination**

Excretion of the metabolites is primarily renal.

Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations. After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

A single oral dose of ramipril produced an undetectable level of ramipril and its metabolite in breast milk. However the effect of multiple doses is not known.

Patients with renal impairment (see section 4.2)

Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment (see section 4.2)

In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

5.3 Preclinical safety data

Oral administration of ramipril has been found to be devoid of acute toxicity in rodents and dogs. Studies involving chronic oral administration have been conducted in rats, dogs and monkeys. Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species.

As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d. Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects.

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.

Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For all PL 33410/0033-36 the following excipients are present

- Hypromellose
- Pregelatinised starch
- Maize starch
- Microcrystalline cellulose
- Colloidal anhydrous silica
- Sodium stearyl fumarate

Additionally for PL 33410/0034

Yellow Iron Oxide (E172)

Additionally for PL 33410/0035

Red Iron Oxide (E172)
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
3 years.

6.4 **Special precautions for storage**
Store below 30°C. Keep the blister in the outer carton in order to protect from light.

6.5 **Nature and contents of container**
PVC/Aluminium blisters containing tablets. Available in pack of 28 tablets.

6.6 **Special precautions for disposal**
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland.

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 33410/0033
PL 33410/0034
PL 33410/0035
PL 33410/0036

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/08/2010

10 **DATE OF REVISION OF THE TEXT**
09/08/2010
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ramiplril 1.25 mg, 2.5 mg, 5 mg and 10 mg Tablets
(Ramiplril)

Read all of this leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets worse or, if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ramiplril Tablets are and what they are used for
2. Before you take Ramiplril Tablets
3. How to take Ramiplril Tablets
4. Possible side effects
5. How to store Ramiplril Tablets
6. Further information

1. WHAT RAMIPLRIL TABLETS ARE AND WHAT THEY ARE USED FOR

Ramiplril Tablets contain a medicine called ramiplril. This belongs to a group of medicines called ACE inhibitors (Angiotension Converting Enzyme Inhibitors).

Ramiplril Tablets work by:
• Decreasing your body’s production of substances that could raise your blood pressure
• Making your blood vessels relax and widen
• Making it easier for your heart to pump blood around your body.

Ramiplril Tablets can be used:
• To treat high blood pressure (hypertension)
• To reduce the risk of you having a heart attack or stroke
• To reduce the risk or delay the worsening of kidney problems (whether or not you have diabetes)
• To treat your heart when it cannot pump enough blood to the rest of your body (heart failure)
• As treatment following heart attack (myocardial infarction) complicated with heart failure.

2. BEFORE YOU TAKE RAMIPLRIL TABLETS

Do not take Ramiplril Tablets:
• If you are more than 3 months pregnant (It is also better to avoid Ramiplril Tablets in early pregnancy – see pregnancy section).
• If you are allergic (hypersensitive) to ramiplril, any other ACE inhibitor medicine or any of the ingredients of Ramiplril Tablets listed in section 6.
• Signs of an allergic reaction may include a rash, swelling or breathing problems, swelling of your lips, face, throat or tongue
• If you have ever had a severe allergic reaction called “angioedema”. The signs include itching, hives (urticaria), red marks on the hands, feet and throat, swelling of the throat and tongue, swelling around the eyes and lips, difficulty breathing and swallowing
• If you are having dialysis or any other type of blood filtration. Depending on the machine that is used, Ramiplril Tablets may not be suitable for you
• If you have kidney problems where the blood supply to your kidneys is reduced (renal artery stenosis)
• If your blood pressure is abnormally low or unstable. Your doctor will need to make this assessment.
• Do not take Ramiplril Tablets if any of the above applies to you. If you are not sure, talk to your doctor before taking Ramiplril Tablets.

Take special care with Ramiplril Tablets:
Check with your doctor or pharmacist before taking your medicine:
• If you have heart, liver or kidney problems
• If you have lost a lot of body salts or fluids through being sick (vomiting), having diarrhoea, sweating more than usual, being on a low salt diet, taking diuretics (water tablets) for a long time or having had dialysis
• If you are going to have treatment to reduce your allergy to bee or wasp stings (desensitization)
• If you are going to receive an anesthetic. This may be given for an operation or any dental work. You may need to stop your Ramiplril Tablets treatment one day beforehand. Ask your doctor for advice
• If you have had high amounts of potassium in your blood (shown in blood test results)
• If you have collagen vascular disease such as scleroderma or systemic lupus erythematosus

You must tell your doctor if you think you are or might become pregnant. Ramiplril Tablets are not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

Children

Ramiplril Tablets are not recommended for use in children and adolescents below 18 years of age because there is no information available in this population.

If any of the above applies to you (or you are not sure), talk to your doctor before taking Ramiplril Tablets.

Taking Ramiplril Tablets with other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription (including herbal medicines). This is because Ramiplril Tablets can affect the way some other medicines work. Also some medicines can affect the way Ramiplril Tablets work:

Please tell your doctor if you are taking any of the following medicines. They can make Ramiplril Tablets work less well:
• Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indomethacin and aspirin)

Medicines used for the treatment of low blood pressure, shock, cardiac failure, asthma or other medicines such as epinephrine, metanorelin or adrenaline.
Your doctor will need to check your blood pressure.

Please tell your doctor if you are taking any of the following medicines. They can increase the chance of getting side effects if you take them with Ramiplril Tablets:
• Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indomethacin and aspirin)

Medicines for cancer (chemotherapy)

Medicines to stop the rejection of organs after a transplant such as ciclosporin

Diuretics (water tablets) such as furosemide

Medicines which can increase the amount of potassium in your blood such as spironactone, trantererene, amiodarone, potassium salts and heparin (for thinning blood)

Steroid medicines for inflammation such as prednisolone

Allopurinol (used to lower the uric acid in your blood)

Propanolol (for heart rhythm problems)

Please tell your doctor if you are taking any of the following medicines. They may be affected by Ramiplril Tablets:
• Medicines for diabetes such as oral glucose lowering medicines and insulin. Ramiplril Tablets may lower your blood sugar amount. Check your blood sugar amount closely while taking Ramiplril Tablets
• Lithium (for mental health problems). Ramiplril Tablets may increase the amount of lithium in your blood. Your lithium amount will need to be closely checked by your doctor.

If any of the above applies to you (or you are not sure), talk to your doctor before taking Ramiplril Tablets.

Taking Ramiplril Tablets with food and alcohol
• Drinking alcohol with Ramiplril Tablets may make you feel dizzy or light-headed. If you are concerned about how much you can drink while you are taking Ramiplril Tablets, discuss this with your doctor, as medicines used to reduce blood pressure and alcohol can have additive effects.

Ramiplril Tablets may be taken with or without food.
Pregnancy and breast-feeding

Pregnancy
You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Ramipril Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Ramipril Tablets. Ramipril Tablets are not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding
Tell your doctor if you are breast-feeding or about to start breast-feeding. Ramipril Tablets are not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
You may feel dizzy while taking Ramipril Tablets. This is more likely to happen when you start taking Ramipril Tablets or start taking a higher dose. If this happens, do not drive or use any tools or machines.

Important information about some of the ingredients of Ramipril Tablets:
Ramipril 2.5mg Tablets and Ramipril 5mg Tablets contain a preservative (E172) which may cause allergic reactions.

3. HOW TO TAKE RAMIPRIL TABLETS
Always take Ramipril Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine
- Take this medicine by mouth at the same time of the day each day.
- Swallow the tablets whole with liquid.
- Do not crush or chew the tablets.

How much to take
Treatment of high blood pressure
- The usual starting dose is 1.25 mg or 2.5 mg once daily.
- Your doctor may adjust the amount you take until your blood pressure is controlled.
- The maximum dose is 10 mg once daily.
- If you are already taking diuretics (water tablets), your doctor may stop or reduce the amount of the diuretic you take before beginning treatment with Ramipril Tablets.

To reduce the risk of you having a heart attack or stroke
- The usual starting dose is 2.5 mg once daily.
- Your doctor may then decide to increase the amount you take.
- The usual dose is 10 mg once daily.

Treatment to reduce or delay the worsening of kidney problems
- You may be started on a dose of 1.25 mg or 2.5 mg once daily.
- Your doctor will adjust the amount you are taking.
- The usual dose is 5 mg or 10 mg once daily.
Treatment of heart failure

- The usual starting dose is 1.25 mg once daily.
- Your doctor will adjust the amount you take.
- The maximum dose is 10 mg daily. Two administrations per day are preferable.

Treatment after you have had a heart attack

- The usual starting dose is 1.25 mg once daily to 2.5 mg twice daily.
- Your doctor will adjust the amount you take.
- The usual dose is 10 mg daily. Two administrations per day are preferable.

Elderly

Your doctor will reduce the initial dose and adjust your treatment more slowly.

If you take more Ramipril tablets than you should

Tell a doctor or go to the nearest hospital casualty department straight away. Do not drive to the hospital, get somebody else to take you or call for an ambulance. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take Ramipril tablets

- If you miss a dose, take your normal dose when it is next due.
- Do not take a double dose to make up for a forgotten tablet.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

If you stop taking Ramipril tablets

If you are having no problems with Ramipril Tablets do not stop taking them without talking to your doctor first.

If you have any questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ramipril tablets can cause side effects, although not everybody gets them.

Stop taking Ramipril tablets and see a doctor straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:

- Swelling of the face, lips or throat which makes it difficult to swallow or breathe, as well as itching and rashes. This could be a sign of a severe allergic reaction to Ramipril tablets.
- Severe skin reactions including rash, ulcers in your mouth, worsening of a pre-existing skin disease, redness, blistering or detachment of skin (such as Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme).

Tell your doctor immediately if you experience:

- Faster heartbeat, sweating or forced heart beat (palpitations), chest pain, tightness in your chest or more serious problems including heart attack and stroke.
- Shortness of breath or a cough. These could be signs of lung problems.
- Bruising more easily, bleeding for longer than normal, any sign of bleeding (e.g. bleeding from the gums), purple spots blooming on the skin or getting lesions more easily than usual, sore throat and fever, feeling tired, faint, dizzy or having pale skin. These can be signs of blood or bone marrow problems.
- Severe stomach pain which may reach through to your back. This could be a sign of pancreatitis (inflammation of the pancreas).
- Fever, chills, tiredness, loss of appetite, stomach pain, feeling sick, yellowing of your skin or eyes (jaundice). These can be signs of liver problems such as hepatitis (inflammation of the liver) or liver damage.

Other side effects include:

Please tell your doctor if any of the following gets serious or lasts longer than a few days.

Common (affects less than 1 in 10 people)

- Headache or feeling tired
- Feeling dizzy: This is more likely to happen when you start taking Ramipril tablets or start taking a higher dose.
- Fainting, hypotension (abnormally low blood pressure), especially when you stand up or sit up quickly.
- Dry thread cough, inflammation of your mouth (soreness) or bronchitis, shortness of breath.
- Stomach or gut pain, diarrhoea, indigestion, feeling or being sick.
- Skin rash with or without raised area.
- Chest pain.
- Cramps or pain in your muscles.
- Blood tests showing more potassium than usual in your blood.

Uncommon (affects less than 1 in 100 people)

- Balance problems (vertigo).
- Itching and unusual skin sensations such as numbness, tingling, pricking, burning or creeping on your skin (paraesthesia).
- Loss or change in the way things taste.
- Sleep problems.
- Feeling depressed, anxious, more nervous than usual or restless.
- Blocked nose, difficulty breathing or worsening of asthma.
- A swelling in your gut called "intestinal angioedema" presenting with symptoms like abdominal pain, vomiting and diarrhoea.
- Heartburn, constipation or dry mouth.
- Passing more water (urine) than usual over the day.
- Sweating more than usual.
- Loss or decrease of appetite (anorexia).
- Increased or irregular heartbeat.
- Swollen ankles and legs. This may be a sign of your body holding on to more water than usual.
- Tinnitus.
- Blurred vision.
- Pain in your joints.
- Fever.
- Sexual inability in men; reduced sexual desire in men or women.
- An increased number of certain white blood cells (eosinophilia) found during a blood test.
- Blood tests showing changes in the way your liver, pancreas or kidneys are working.

Rare (affects less than 1 in 1,000 people)

- Feeling shaky or confused.
- Red and swollen tongue.
- Severe blushing or peeling of the skin, itchy, lumpy rash.
- Nail problem (e.g. loosening or separation of a nail from its bed).
- Skin rash or bruising.
- Blotches on your skin and cold extremities.
- Red, itchy, swollen or watery eyes.
- Disturbed hearing and ringing in your ears.
- Feeling weak.
- Blood tests showing a decrease in the number of red blood cells, white blood cells or platelets or in the amount of haemoglobin.

Very rare (affects less than 1 in 10,000 people)

- Being more sensitive to the sun than usual.

Other side effects reported:

Please tell your doctor if any of the following gets serious or lasts longer than a few days.

- Difficulty concentrating.
- Swollen mouth.
- Blood tests showing too few blood cells in your blood.
- Blood tests showing less sodium than usual in your blood.
- Fingers and toes changing colour when you are cold and then tingling or feeling painful when you warm up (Raynaud's phenomenon).
- Breast enlargement in men.
- Slowed or impaired reactions.
- Burning sensation.
- Change in the way things smell.
- Hair loss.

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
4. HOW TO STORE RAMIPRIL TABLETS

Keep out of the reach and sight of children.

Do not use Ramipril tablets after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Store below 30 °C. Keep the blister in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

These measures will help protect the environment.

6. FURTHER INFORMATION

What Ramipril Tablets contain:

- The active substance is Ramipril.
- Ramipril 1.25 mg Tablets contain 1.25 mg ramipril.
- Ramipril 2.5 mg Tablets contain 2.5 mg ramipril.
- Ramipril 5 mg Tablets contain 5 mg ramipril.
- Ramipril 10 mg Tablets contain 10 mg ramipril.

- The other ingredients are hypromellose, premagnesium stearate, maize starch, microcrystalline cellulose, colloidal anhydrous silica, sodium starch glycolate. The 2.5 mg tablets also contain yellow iron oxide (E172) and the 5 mg tablets also contain red iron oxide (E173).

Remember: This medicine is for you. Only a doctor can prescribe it to you. Never give it to someone else. It may harm them, even if they have the same symptoms as you.

What Ramipril Tablets look like and contents of the pack:

Ramipril tablets are presented in blister packs of 28 tablets and come in 4 strengths:
- Ramipril 1.25 mg Tablets (White, capsule shaped, bicorner, uncoated tablets debossed with 1 25 on one side and central breakline on other side).
- Ramipril 2.5 mg Tablets (Yellow, capsule shaped, bicorner, uncoated tablets debossed with 2.5 on one side and central breakline on other side).
- Ramipril 5 mg Tablets (Pink, capsule shaped, bicorner, uncoated tablets debossed with 5 on one side and central breakline on other side).
- Ramipril 10 mg Tablets (White, capsule shaped, bicorner, uncoated tablets debossed with 10 on one side and central breakline on other side).

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Manufacturer:

Repharm Limited, Vale of Belvoir, Ashby-Under-Lyne, Leekashire, OL7 9ER, United Kingdom

Marketed and Distributed By:

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This leaflet was last approved in May/1111

This leaflet does not contain all the information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.