RAMIPRIL 2.5MG CAPSULES (RAMIPRIL)  
PL 10622/0125

RAMIPRIL 5MG CAPSULES (RAMIPRIL)  
PL 10622/0126

RAMIPRIL 10MG CAPSULES (RAMIPRIL)  
PL 10622/0127

UKPAR

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The MHRA granted Pliva Pharma Ltd Marketing Authorisations (licences) for the medicinal products Ramipril 2.5mg Capsules (PL 10622/0125), Ramipril 5mg Capsules (PL 10622/0126) and Ramipril 10mg Capsules (PL 10622/0127) on 26th June 2006. These prescription only medicines (POM) are used to treat patients with high blood pressure or congestive heart failure and to reduce the risk of heart attack or stroke.

Ramipril Capsules contain the active ingredient ramipril, which is an Angiotensin Converting Enzyme (ACE) Inhibitor, which helps to relax artery walls.

The data presented to the MHRA, pre licensing, demonstrated that Ramipril Capsules are equivalent to the approved products, Tritace Capsules. Ramipril Capsules can therefore be used interchangeably with Tritace Capsules.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Ramipril capsules outweigh the risks. Hence, Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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Overall conclusions and risk benefit assessment Page 18
INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Ramipril 2.5mg Capsules (PL 10622/0125), Ramipril 5mg Capsules (PL 10622/0126) and Ramipril 10mg Capsules (PL 10622/0127) to Pliva Pharma Ltd on 26th June 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1 [formerly article 10.1(a)(iii)] of Directive 2001/83/EC, claiming essential similarity to the original products Tritace capsules.

The products contain the active ingredient ramipril and are indicated for the treatment of hypertension and heart failure and reduction of risk of myocardial infarction, cardiovascular death or revascularisation procedures in patients over 55 or with clinical evidence of cardiovascular disease.

Ramipril is an ACE Inhibitor which 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.
PHARMACEUTICAL ASSESSMENT

I. INTRODUCTION

These are national abridged applications submitted under article 10a [formerly article 10(a)(iii)] of Directive 2001/83/EC and claiming essential similarity to Tritace 2.5mg, 5mg and 10mg Capsules, marketed in the UK by Hoescht Marion Roussel (PL 13402/0022-24). Tritace was first approved in the UK on 28 November 1989 (PL 00086/0130-132).

Ramipril is an angiotensin converting enzyme (ACE) inhibitor indicated for treatment of hypertension and heart failure and reduction of risk of myocardial infarction, cardiovascular death or revascularisation procedures in patients over 55 or with clinical evidence of cardiovascular disease. Dosage varies with indication and is in the range 1.25mg to 10mg daily, in one or two doses.

II. DRUG SUBSTANCE

Information on the suitability of the drug substance has been provided by way of a drug master file (DMF). A suitable letter of access to the confidential data therein has been provided.

The drug substance specification applied by the finished product manufacturer is tighter in relation to named impurities than that of the Active Ingredient manufacturer (AIM) and pharmacopoeia. Methods used for control of the drug substance by the finished product manufacturer have been described and evidence of their suitability for control of ramipril from the source has been provided.

III. DRUG PRODUCT

III.1 Description and Qualitative Composition of the Drug Product

Table 1: Composition of Ramipril Capsules

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Reference to standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active ingredient:</strong></td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>EP</td>
</tr>
<tr>
<td><strong>Excipients:</strong></td>
<td></td>
</tr>
<tr>
<td>Pregelatinised starch</td>
<td>EP</td>
</tr>
<tr>
<td><strong>Capsule shell body:</strong></td>
<td></td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>EP</td>
</tr>
<tr>
<td>Gelatin</td>
<td>EP</td>
</tr>
<tr>
<td><strong>Capsule shell cap:</strong></td>
<td></td>
</tr>
<tr>
<td>Patent blue V (E131)</td>
<td>CFR21</td>
</tr>
<tr>
<td>Azorubine (Carmoisine) E122</td>
<td>CFR21</td>
</tr>
<tr>
<td>Quinoline yellow E104</td>
<td>Ph Fr</td>
</tr>
<tr>
<td>Red iron oxide</td>
<td>CFR21</td>
</tr>
<tr>
<td>Yellow iron oxide</td>
<td>CFR21</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>EP</td>
</tr>
<tr>
<td>Gelatin</td>
<td>EP</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>EP</td>
</tr>
</tbody>
</table>
The products are hard gelatin capsules filled with powder containing a mixture of ramipril and pregelatinised starch.

The capsules are packed into PVC/Aclar/aluminium blister packs or in round white HDPE bottles (60ml and 200ml). In these applications, the MA applicant does not propose to market HDPE packs.

Table 2: Appearance of Ramipril Capsules

<table>
<thead>
<tr>
<th></th>
<th>1.25mg</th>
<th>2.5mg</th>
<th>5mg</th>
<th>10mg</th>
<th>1.25mg</th>
<th>2.5mg</th>
<th>5mg</th>
<th>10mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body</td>
<td>White</td>
<td>White</td>
<td>White</td>
<td>White</td>
<td>Yellow</td>
<td>Orange</td>
<td>Red</td>
<td>Blue</td>
</tr>
<tr>
<td>Cap</td>
<td>Yellow</td>
<td>Orange</td>
<td>Red</td>
<td>Blue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

The colours used to help distinguish the different strengths are the same as those described by the brand leader.

Clinical Trial Formulae

Bioequivalence studies were conducted with the 10mg strength capsule of identical composition to that described above.

III.2 Pharmaceutical Development

Ramipril is ‘slightly soluble’ in water and, at worst, 10mg ramipril should dissolve in 10ml water. Solubility is increased in 0.1M HCl. Absolute bioavailabilities of ramipril and ramiprilat are described as 28% and 44%, respectively. In view of the nature of the formulation and the solubility of the pro-drug, release of drug substance from the capsule is not anticipated to be a rate limiting factor in the in vivo absorption of ramipril.

Comparative impurities profiles have been provided between generic ramipril capsules and Tritace (UK) 10mg and Altace (Canada), 2.5mg & 5mg. Total impurities are generally similar between products of the same strength.

The development pharmaceutics section includes brief details on the rationale for the formulation.

The development of the dissolution method and optimisation of physical properties of the drug substance have not been discussed but the product is an immediate release capsule containing a slightly soluble drug substance and release of the active ingredient from the dose form is not anticipated to be critical to bioavailability.

Omission of further information on the development of the product is accepted on the basis of the nature of the formulation, the method of manufacture and supporting data provided in the rest of the dossier.

III.3 Manufacture
III.3.1 Manufacturer(s)
Details of the product manufacturer have been provided.

Batch release in the EEA is conducted either at Dragenopharm Apotheker Puschl GmbH or Chanelle Medical Ltd, Co. Galway, Ireland.

III.3.2 Batch Formula
Batch sizes have been described for, 2.5mg, 5mg and 10mg strengths.

IV.3.3 Description of Manufacturing Process and Process Controls
The manufacturing process is a conventional pharmaceutical unit process.

Manufacturing equipment and mixing times are described and a clear flow diagram of the process has been provided. In-process controls have been provided and are acceptable.

The process validation protocol for commercial production has been provided. The protocol outlines the sampling procedure and acceptance limits and these are appropriate.

A clear description of this standard manufacturing process has been provided.

III.4 Control of Excipients

III.4.1 Specifications
Pre-gelatinised starch, gelatin, polysorbate and sodium chloride are controlled in accordance with Ph Eur.

Manufacturer’s specifications have been provided for gelatins type A and B used in shell manufacture and for colours quinoline yellow, azorubicine, patent blue V, red & yellow iron oxide.

III.4.2 Excipients of Human or Animal Origin
The capsule shell supplier has declared that gelatin of bovine and porcine origin may be used. Porcine gelatin is outwith the scope of the CPMP TSE requirements. A declaration has been provided that all bovine derived gelatin is purchased from suppliers holding an EDQM Certificate of Suitability.

III.5 Control of Drug Product

III.5.1 Specification(s)
Finished Product Specifications have been provided and are acceptable.

III.5.2 Analytical Procedures
The methods have been described in adequate detail.

**III.5.3 Validation of Analytical Procedures**
Supporting validation data confirm the suitability of the analytical methods proposed.

**III.5.4 Batch Analyses**
Method references indicate that batches were tested using the validated methods described above. All batches comply with the proposed specification.

**III.5.5 Characterisation of Impurities**
Characterisation and proposed control limits of degradants in the finished product are acceptable.

**III.5.6 Justification of Specification(s)**
The controls included in the specification are appropriate for a product of this nature. The applicant has stated that all batches will be tested in full against the specification. The specification does not control all potential ramipril impurities but the process impurities are appropriately controlled in the drug substance specification and limits have been set for potential degradants. This is acceptable.

Control limits are acceptable and are in line with pharmacopoeial and regulatory requirements.

**III.6 Reference Standards or Materials**
Reference standards used in validation of the analytical methods have been described.

**III.7 Container Closure System**
Primary container configurations are PVC/Aclar/aluminium blisters and HDPE (60ml and 200ml) bottles with polypropylene cap.

The product manufacturer’s specifications include controls for dimensions and water permeation (PVC/Aclar and HDPE bottle) and polymer identity. These are acceptable.

A statement of compliance with Directive 2002/72 has been provided by the manufacturers of the packaging components.

**III.8 Stability**
Pilot batches of each strength have been entered into stability studies under long term, intermediate and accelerated conditions of storage. The capsules have been stored in both proposed packaging types (HDPE and PVC/Aclar blisters).

**III.8.1 Stability Summary and Conclusion**
The following conclusions can be drawn:
The products are unstable under intermediate and accelerated conditions of storage.

Potency loss is very variable in batches on long-term storage.

The lower strength capsules (2.5mg) are less stable than the 5mg and 10mg capsules as evidenced by potency and total impurities results.

A shelf-life of 12 months (2.5mg strength) and 18 months (5mg & 10mg strengths) is proposed with the storage requirement of ‘do not store above 25°C’. This is supported by the data provided.

III.8.2 Post-approval Stability Protocol and Stability Commitments

A suitable stability protocol has been provided. The first three batches of each strength in both pack configurations will be entered into stability studies under long-term and intermediate storage conditions. Details of the specification and sample times have been provided and are acceptable.

IV. REGIONAL INFORMATION

V ASSESSOR’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

V.1 Other information

Not provided.

V.1.2 Bioanalytical methods

Ramipril and ramiprilat were determined in human plasma using a validated method.

V.1.3 Bioavailability, bioequivalence

Two bioequivalence studies have been presented in the dossier. Both are single dose, randomised, cross-over designs in which ramipril 10mg is administered from test and reference products in healthy male volunteers. A wash out period of 42 days was employed in both studies. Ramipril 10mg capsules were used as the test product in both studies. The reference products differed in these studies being Altace, Aventis, Canada, and Tritace, Aventis, UK. The latter study is therefore the pivotal study for the claim of essential similarity with the UK brand leader.

This was a randomised, single dose, cross-over bioequivalence study conducted in 26 (+6) healthy male volunteers. The test product was Ramipril 10mg Capsules and the reference product was Tritace 10mg Capsules, Aventis Pharma, UK.

The comparative statistics for test and reference products are summarised in table 3 below:

Table 3: Comparative statistics of the main pharmacokinetic parameters of ramiprilat after administration of 10 mg ramipril by means of the test and reference (Tritace®) formulations (N=26).
<table>
<thead>
<tr>
<th></th>
<th>$\mu_T$</th>
<th>$\mu_R$</th>
<th>$\mu_T : \mu_R$ (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untransformed</strong></td>
<td><strong>data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$ [ng/mL]</td>
<td>16.700</td>
<td>19.078</td>
<td>87.54</td>
<td>78.42 - 97.72</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{tlast}}$ [ng.h.mL]</td>
<td>299.157</td>
<td>309.957</td>
<td>96.52</td>
<td>91.72 - 101.56</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ [ng.h/mL]</td>
<td>401.130</td>
<td>405.955</td>
<td>98.81</td>
<td>93.17 - 104.80</td>
</tr>
<tr>
<td><strong>Potency adjusted data (to 10 mg ramipril)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$ [mg/mL]</td>
<td>17.400</td>
<td>18.704</td>
<td>93.01</td>
<td>83.32 - 103.82</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{tlast}}$ [ng.h.mL]</td>
<td>311.622</td>
<td>303.879</td>
<td>102.55</td>
<td>97.45 - 107.91</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ [ng.h/mL]</td>
<td>417.844</td>
<td>397.995</td>
<td>104.99</td>
<td>98.99 - 111.35</td>
</tr>
</tbody>
</table>

Least-square adjusted (estimated) true treatment means ($\mu_T$ and $\mu_R$) and ratio of the true treatment means ($\mu_T : \mu_R$) of the main pharmacokinetic variables after p.o. doses of 10mg ramipril administered by either the investigational (T:test) or the reference formulation (R:reference).

The assay values of the test and reference products differ by some 6% and ‘potency adjustment’ data have also been provided. The untransformed data indicate that the point estimates and 90% confidence intervals for the AUC (0-tlast) and AUC (0-inf.) ratios of test: reference products are within the usual acceptance ranges for bioequivalence. However, the untransformed Cmax for the test product is slightly lower than the reference product. The applicant’s explanation for this apparent difference is the difference in assay results between test and reference products, 9.6mg and 10.2mg per capsule, respectively.

‘Normalisation’ of the data to the label dose is not usually conducted in these studies and no provision is made for this transformation in the bioequivalence guidelines. Never-the-less, the untransformed data indicate that the test and reference products can be considered bioequivalent with respect to the extent of absorption and the solubility of the drug substance and nature of the formulation do not suggest that release of the active ingredient from the dosage form would be critical to its bioavailability. The clinical implications of the Cmax results are considered in the medical assessment report.

The data using Altace as reference were similar and demonstrated slightly lower bioavailability of ramipril from the test product as compared to the reference, but point estimates and 90% confidence intervals for ratios of AUC and Cmax for untransformed data were within the usual acceptance limits for bioequivalence.

The conclusions of the bioequivalence study with 10mg capsules have been extrapolated to the other strengths of capsules. The justification is that the ramiprilat 24 hours AUC (but not Cmax) is dose proportional over the range 2.5mg –20mg.
Product composition and dissolution profiles across the range of strengths support extrapolation of the bioequivalence results from the study with 10mg ramipril, provided that kinetics are linear over the entire dosage range.

V.1.4 Essential similarity

The applicant’s products contain the same quantitative and qualitative composition with respect to the active ingredient and are the same dosage form. The excipients are conventional and do not pose safety concerns. In the bioequivalence study, the test product displayed a slightly lower Cmax than the reference product but the untransformed AUC’s were within conventional acceptance limits. The claims of essential similarity may be accepted.

V.2.1 Administrative

V.2.2 Comment on Expert report

The expert report is by a pharmacist and regulatory affairs manager. The report is generally non critical.

V.2.3 MAA form

Summary of Product Characteristics

Satisfactory.

Patient Information Leaflet

Satisfactory.

Labels

Satisfactory

VI ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

Marketing Authorisations may be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
1. **INTRODUCTION**

This is a national abridged application for generic ramipril 2.5mg, 5mg and 10mg Capsules. Essential similarity has been claimed with the reference product (Tritace) PL – 13402/0022 – 0024. The applicant has provided signed declaration for TSE compliance.

2. **BACKGROUND**

ATC code – C09A05

Ramipril is a well known ACE inhibitor. It has been used for the treatment of hypertension, congestive heart failure, reduction of risk of myocardial infarction, stroke and other cardiovascular complications and prevention of diabetic nephropathy.

3. **INDICATIONS**

“Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous, MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings: hypertension (systolic blood pressure > 160mmHg or diastolic blood pressure > 90mmHg); high total cholesterol (>5.2mmol/L); low HDL (<0.9 mmol/L); current smoker; known microalbuminuria; clinical evidence of previous vascular disease.

The treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril has been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.”

4. **DOSE & DOSE SCHEDULE**

“Posology and method of administration

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures:

The recommended initial dose is 2.5mg ramipril once a day. Depending on the tolerability, the dose should be gradually increased. It is therefore recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10mg. The usual maintenance dose is 10mg ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg ramipril once daily.
**Hypertension:**
The recommended initial dosage in patients not on diuretics and without congestive heart failure is 1.25 mg ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 - 5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

**Congestive heart failure:**
Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25 mg once daily. Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting ramipril.

**Post myocardial infarction:**
Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI. The starting dose is 2.5 mg twice a day, which is increased to 5 mg twice a day after 2 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 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5.0 mg twice a day.

Dosage adjustment in renal impairment:
The usual dose of ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 µmol/l). For patients with a creatinine clearance < 30 ml/min (serum creatinine >165 µmol/l) the initial dose is 1.25 mg ramipril once daily and the maximum dose 5 mg ramipril once daily.

In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 µmol/l), the recommended initial dose is also 1.25 mg ramipril once a day, but the maintenance dose should not exceed 2.5 mg ramipril once a day.

**Dosage in hepatic impairment:**
In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

_Elderly:_
Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

_Children:_
Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril capsules should be taken with a glass of water. The absorption of ramipril is not affected by food.”

5. **TOXICOLOGY**

No toxicological data has been submitted and none is required.

6. **CLINICAL PHARMACOLOGY**

The clinical pharmacology of ramipril is known. The applicant has not generated PD and PK data except for bioequivalence studies. This is acceptable as the product has been used clinically for many years.

6.1 **BIOEQUIVALENCE**

Two bioequivalence studies were carried out, one used Altace (Canada) and other Tritace (UK) as the reference product. The details of the study with Tritace is given below.

The comparative bioavailability was evaluated in a single dose, randomised, blinded, crossover study in 32 (29 completed both periods of cross over) healthy male volunteers. The 10mg capsule of ramipril was compared to the reference formulation (Tritace® 10mg capsules (Aventis Pharma).

In this study, the kinetic parameters of ramiprilat were used to establish the bioequivalence standards whereas ramipril data were provided for information purposes. The drug content of the test product differed from the reference product by more than 5% hence the kinetic parameters were adjusted to 100% label claim on the basis of measured content of the dosage form.

The results based on ramiprilat data are shown below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric LS Means</th>
<th>Ratio</th>
<th>90% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Uncorrected Cmax</td>
<td>16.7</td>
<td>19.08</td>
<td>87.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td><strong>AUC 0-t last</strong></td>
<td>299.16</td>
<td>309.96</td>
<td>96.52</td>
</tr>
<tr>
<td><strong>AUC0-∞</strong></td>
<td>401.13</td>
<td>405.95</td>
<td>98.81</td>
</tr>
<tr>
<td><strong>Corrected Cmax</strong></td>
<td>17.396</td>
<td>18.704</td>
<td>93.01</td>
</tr>
<tr>
<td><strong>AUC0-t last</strong></td>
<td>311.622</td>
<td>303.879</td>
<td>102.55</td>
</tr>
<tr>
<td><strong>AUC0-∞</strong></td>
<td>417.844</td>
<td>397.996</td>
<td>104.99</td>
</tr>
</tbody>
</table>

The study was conducted according to the GCP guidance.

**Assessor’s Comments:** Although the lower limit of CI for Cmax was marginally lower than the acceptable range, this was not considered significant as the AUC values were within the range for bioequivalence. The Canadian study also showed bioequivalence both on Cmax and AUC criteria. The company’s argument regarding potency-adjusted bioequivalence is unusual and is not the criteria defined in the guideline. However as AUCt is the most reliable indicator of absorption it is concluded that the bioequivalence of the product has been shown.

7. **EFFICACY**

No new data have been submitted and none are required. The clinical use of ramipril is well established.

8. **SAFETY**

No new data have been submitted and none are required. The safety profile of ramipril is well known.

9. **EXPERT REPORT**

The clinical expert report was written by a clinical pharmacologist/internist. The report was non-critical. The expert concludes that the products are bioequivalent to the reference product. The expert has adequately summarised the clinical use of ramipril in various clinical conditions.

10. **SUMMARY OF PRODUCT CHARACTERISTICS**

The SPC is identical to the SPC of the reference product (Tritace).

11. **PATIENT INFORMATION LEAFLET**

The patient information leaflet is satisfactory.

12. **LABELLING**
Satisfactory.

13. DISCUSSION

Ramipril is well known ACE inhibitor and has been in clinical use for many years. The bioequivalence of the product has been shown. The SPC is identical to the SPC of the reference product (Tritace).
Although the bioequivalence study has been done only with 10mg tablets, the expert’s argument that the dose proportionality for ramiprilat has been shown over the 2.5 – 20 mg dose and this can be accepted to apply to lower dose strengths is accepted by the assessor in view of the extensive clinical experience with ramipril.

14. CONCLUSIONS

There is no clinical objection to the grant of marketing authorisations for these products.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ramipril Capsules 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 have been supplied with these applications and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant’s Ramipril Capsules and the originator products, Tritace Capsules.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Tritace Capsules.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Clinical experience with ramipril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 26/07/2002</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 05/09/2002</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information relating to the dossier on 26/03/2003, 16/06/2003, 13/08/2003, 27/01/2004 and 31/07/2005.</td>
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<td>5</td>
<td>The application was determined on 26/06/2006</td>
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RAMIPRIL 2.5MG, 5MG & 10MG CAPSULES (RAMIPRIL)
PL 10622/0125-7

STEPS TAKEN AFTER ASSESSMENT

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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1. NAME OF THE MEDICINAL PRODUCT

Ramipril 2.5mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2.5mg ramipril.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Size 4 capsules with white body and orange cap.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings: hypertension (systolic blood pressure > 160mmHg or diastolic blood pressure > 90mmHg); high total cholesterol (>5.2 mmol/L); low HDL (<0.9 mmol/L); current smoker; known microalbuminuria; clinical evidence of previous vascular disease.

The treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril has been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.
4.2. Posology and method of administration

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures:
The recommended initial dose is 2.5mg ramipril once a day. Depending on the tolerability, the dose should be gradually increased. It is therefore recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10mg. The usual maintenance dose is 10mg ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg ramipril once daily.

Hypertension:
The recommended initial dosage in patients not on diuretics and without congestive heart failure is 1.25 mg ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 - 5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

Congestive heart failure:
Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25 mg once daily. Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting ramipril.

Post myocardial infarction:
Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 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 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5.0 mg twice a day.
Dosage adjustment in renal impairment:
The usual dose of ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 μmol/l). For patients with a creatinine clearance < 30 ml/min (serum creatinine > 165 μmol/l) the initial dose is 1.25 mg ramipril once daily and the maximum dose 5 mg ramipril once daily.

In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 μmol/l), the recommended initial dose is also 1.25 mg ramipril once a day, but the maintenance dose should not exceed 2.5 mg ramipril once a day.

Dosage in hepatic impairment:
In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

Elderly:
Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

Children:
Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril capsules should be taken with a glass of water. The absorption of ramipril is not affected by food.

4.3. Contraindications

Hypersensitivity to ramipril or any of the excipients. History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients. Pregnancy. Lactation.

4.4. Special warnings and special precautions for use

Warnings:

Ramipril should not be used in patients with aortic or mitral valve stenosis or outflow obstruction.

Precautions:

Assessment of renal function:
Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment.

Impaired renal function:
Patients with renal insufficiency may require reduced or less frequent doses of ramipril; their renal function should be closely monitored. In the majority, renal function will not alter. There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis.

Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.

**Impaired liver function:**
As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

**Symptomatic hypotension:**
In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of ramipril as well as after increasing the dose of ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with ramipril.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with ramipril may usually be continued following restoration of effective blood volume and blood pressure.

**Surgery/anaesthesia:**
In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment.

**Agranulocytosis and bone marrow depression:**
In patients on angiotensin converting enzyme inhibitors agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count, haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and anti metabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

**Hyperkalaemia:**
Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

4.5. **Interaction with other medicinal products and other forms of interaction**

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If ramipril is given with lithium, an increase in serum lithium concentration may occur.

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

4.6. **Pregnancy and lactation**

Pregnancy should be excluded before start of treatment with ramipril and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased utero-placental perfusion. There is also a potential risk of fetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri-post natal studies increased renal pelvic dilatation was observed in the first generation offspring. ACE inhibitors have shown fetotoxicity in some species.
Ramipril should not be used during lactation.

4.7. Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with ramipril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. 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

Generally, adverse reactions have been mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

*Cardiovascular:*
Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of ramipril and after an increase in the dose of ramipril. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure. Syncope has also been observed rarely.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

*Renal:*
Treatment with ramipril may impair renal function.

*Gastrointestinal:*
Treatment with ramipril may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea, and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort (sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

*Allergic:*
Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of ramipril.
In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid exanthema and enanthema, hypersensitivity of the skin to light and onycholysis have been observed.

Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.

Angioneurotic oedema:
In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with ramipril must be discontinued and appropriate therapy instituted immediately.

Respiratory tract:
A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

Other adverse reactions:
Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

Laboratory test findings:
Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate.

Serum sodium levels may decrease. Elevation of serum potassium may occur, since ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

4.9. Overdose
In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat
which is a potent and long acting ACE inhibitor. 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. There is evidence suggesting that tissue ACE particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramiprilat appears to have some effects on the kallikrein-kinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive and metabolic activity of ramipril.

Administration of ramipril to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3 - 6 hours after drug intake and has been shown to be maintained for at least 24 hours after usual therapeutic doses.

In a large endpoint study - HOPE - ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous dose-ranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the renin-angiotensin-aldosterone system. This and other studies suggest that ACE inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

5.2. Pharmacokinetic properties

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2 - 4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 - 17 hours for 5 - 10 mg ramipril and markedly longer for lower doses, 1.25 - 2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. 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.
Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.

5.3. Preclinical safety data

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 and higher.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Pregelatinised starch,
Gelatin,
Titanium dioxide (E171),
Red iron oxide (E172),
Yellow iron oxide (E172),
Polysorbate 80 and
Sodium chloride.

6.2. Incompatibilities

None known.

6.3. Shelf life

12 months.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5. Nature and contents of container

PVC/Aclar/aluminium blister packs or HDPE bottle with polypropylene screw cap and permaseal liner containing 7, 21 or 28 tablets.

6.6. Instruction for use and handling and disposal

None.

7. MARKETING AUTHORISATION HOLDER
8. MARKETING AUTHORISATION NUMBER(S)
   PL 10622/0125

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   26/06/2006

10. DATE OF REVISION OF THE TEXT
    26/06/2006
1. NAME OF THE MEDICINAL PRODUCT

Ramipril 5mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5mg ramipril.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Size 4 capsules with white body and red cap.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings: hypertension (systolic blood pressure > 160mmHg or diastolic blood pressure > 90mmHg); high total cholesterol (>5.2 mmol/L); low HDL (<0.9 mmol/L); current smoker; known microalbuminuria; clinical evidence of previous vascular disease.

The treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril has been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.

4.2. Posology and method of administration
Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures:
The recommended initial dose is 2.5mg ramipril once a day. Depending on the tolerability, the dose should be gradually increased. It is therefore recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10mg. The usual maintenance dose is 10mg ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg ramipril once daily.

Hypertension:
The recommended initial dosage in patients not on diuretics and without congestive heart failure is 1.25 mg ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 - 5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

Congestive heart failure:
Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25 mg once daily. Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting ramipril.

Post myocardial infarction:
Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 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 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5.0 mg twice a day.

Dosage adjustment in renal impairment:
The usual dose of ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 µmol/l). For patients with a creatinine clearance < 30 ml/min (serum creatinine >165 µmol/l) the initial dose is 1.25 mg ramipril once daily and the maximum dose 5 mg ramipril once daily.

In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 µmol/l), the recommended initial dose is also 1.25 mg ramipril once a day, but the maintenance dose should not exceed 2.5 mg ramipril once a day.

**Dosage in hepatic impairment:**
In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

**Elderly:**
Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

**Children:**
Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril capsules should be taken with a glass of water. The absorption of ramipril is not affected by food.

### 4.3. Contraindications

Hypersensitivity to ramipril or any of the excipients. History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients. Pregnancy. Lactation.

### 4.4. Special warnings and special precautions for use

**Warnings:**

Ramipril should not be used in patients with aortic or mitral valve stenosis or outflow obstruction.

**Precautions:**

**Assessment of renal function:**
Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment.

**Impaired renal function:**
Patients with renal insufficiency may require reduced or less frequent doses of ramipril; their renal function should be closely monitored. In the majority, renal function will not
There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high flux polyacrylonitrile (‘AN69’) membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis.

Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.

**Impaired liver function:**
As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

**Symptomatic hypotension:**
In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of ramipril as well as after increasing the dose of ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with ramipril.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with ramipril may usually be continued following restoration of effective blood volume and blood pressure.

**Surgery/anaesthesia:**
In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment.

**Agranulocytosis and bone marrow depression:**
In patients on angiotensin converting enzyme inhibitors agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count,
haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and anti metabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

Hyperkalaemia:
Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

4.5. Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If ramipril is given with lithium, an increase in serum lithium concentration may occur.

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

4.6. Pregnancy and lactation

Pregnancy should be excluded before start of treatment with ramipril and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased uteroplacental perfusion. There is also a potential risk of fetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri-post natal studies increased renal pelvic dilatation was observed in the first generation offspring. ACE inhibitors have shown fetotoxicity in some species.

Ramipril should not be used during lactation.
4.7. Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with ramipril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. 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

Generally, adverse reactions have been mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

*Cardiovascular:*Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of ramipril and after an increase in the dose of ramipril. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure. Syncope has also been observed rarely.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

*Renal:*Treatment with ramipril may impair renal function.

*Gastrointestinal:*Treatment with ramipril may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea, and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort (sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatititis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

*Allergic:*Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of ramipril.

In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exantherma and enantherma, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of
Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid exanthema and enanthema, hypersensitivity of the skin to light and onycholysis have been observed.

Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.

**Angioneurotic oedema:**
In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with ramipril must be discontinued and appropriate therapy instituted immediately.

**Respiratory tract:**
A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

**Other adverse reactions:**
Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

**Laboratory test findings:**
Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate.

Serum sodium levels may decrease. Elevation of serum potassium may occur, since ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

### 4.9. Overdose
In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1. Pharmacodynamic properties
Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat which is a potent and long acting ACE inhibitor. 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. There is evidence suggesting that tissue ACE particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramiprilat appears to have some effects on the kallikrein-kinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive and metabolic activity of ramipril.

Administration of ramipril to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3 - 6 hours after drug intake and has been shown to be maintained for at least 24 hours after usual therapeutic doses.

In a large endpoint study - HOPE - ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous dose-ranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the renin-angiotensin-aldosterone system. This and other studies suggest that ACE inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

5.2. **Pharmacokinetic properties**

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2 - 4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 - 17 hours for 5 - 10 mg ramipril and markedly longer for lower doses, 1.25 - 2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. 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.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.
5.3. Preclinical safety data

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 and higher.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Pregelatinised starch,
Gelatin,
Titanium dioxide (E171),
Quinoline yellow (E104),
Azorubine (E122),
Polysorbate 80 and
Sodium chloride.

6.2. Incompatibilities

None known.

6.3. Shelf life

18 months.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5. Nature and contents of container

PVC/Aclar/aluminium blister packs or HDPE bottle with polypropylene screw cap with Permaseal liner containing 7, 21 or 28 tablets.

6.6. Instruction for use and handling and disposal

None.

7. MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
UK.

8. MARKETING AUTHORISATION NUMBER(S)
   PL 10622/0126

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   26/06/2006

10. DATE OF REVISION OF THE TEXT
    26/06/2006
1. NAME OF THE MEDICINAL PRODUCT

Ramipril 10mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10mg ramipril.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Size 4 capsules with white body and blue cap.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings: hypertension (systolic blood pressure > 160mmHg or diastolic blood pressure > 90mmHg); high total cholesterol (>5.2 mmol/L); low HDL (<0.9 mmol/L); current smoker; known microalbuminuria; clinical evidence of previous vascular disease.

The treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril has been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.

4.2. Posology and method of administration
Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures:
The recommended initial dose is 2.5mg ramipril once a day. Depending on the tolerability, the dose should be gradually increased. It is therefore recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10mg. The usual maintenance dose is 10mg ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg ramipril once daily.

Hypertension:
The recommended initial dosage in patients not on diuretics and without congestive heart failure is 1.25 mg ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 - 5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

Congestive heart failure:
Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25 mg once daily. Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting ramipril.

Post myocardial infarction:
Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 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 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5.0 mg twice a day.

Dosage adjustment in renal impairment:
The usual dose of ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 µmol/l). For patients with a creatinine clearance < 30
ml/min (serum creatinine >165 µmol/l) the initial dose is 1.25 mg ramipril once daily and the maximum dose 5 mg ramipril once daily.

In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 µmol/l), the recommended initial dose is also 1.25 mg ramipril once a day, but the maintenance dose should not exceed 2.5 mg ramipril once a day.

Dosage in hepatic impairment:
In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

Elderly:
Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

Children:
Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril capsules should be taken with a glass of water. The absorption of ramipril is not affected by food.

4.3. Contraindications

Hypersensitivity to ramipril or any of the excipients. History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients. Pregnancy. Lactation.

4.4. Special warnings and special precautions for use

Warnings:

Ramipril should not be used in patients with aortic or mitral valve stenosis or outflow obstruction.

Precautions:

Assessment of renal function:
Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment.

Impaired renal function:
Patients with renal insufficiency may require reduced or less frequent doses of ramipril; their renal function should be closely monitored. In the majority, renal function will not alter. There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal
artery stenosis in the single kidney as well as after renal transplantation. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high flux polyacrylonitrile (‘AN69’) membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis.

Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.

Impaired liver function:
As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

Symptomatic hypotension:
In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of ramipril as well as after increasing the dose of ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with ramipril.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with ramipril may usually be continued following restoration of effective blood volume and blood pressure.

Surgery/anaesthesia:
In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment.

Agranulocytosis and bone marrow depression:
In patients on angiotensin converting enzyme inhibitors agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count, haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Regular monitoring of
white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and anti metabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

Hyperkalaemia:
Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

4.5. Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.

When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If ramipril is given with lithium, an increase in serum lithium concentration may occur.

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

4.6. Pregnancy and lactation

Pregnancy should be excluded before start of treatment with ramipril and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased utero-placental perfusion. There is also a potential risk of fetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri-post natal studies increased renal pelvic dilatation was observed in the first generation offspring. ACE inhibitors have shown fetotoxicity in some species.

Ramipril should not be used during lactation.
4.7. Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with ramipril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. 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

Generally, adverse reactions have been mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

Cardiovascular:
Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of ramipril and after an increase in the dose of ramipril. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure. Syncope has also been observed rarely.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

Renal:
Treatment with ramipril may impair renal function.

Gastrointestinal:
Treatment with ramipril may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea, and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort (sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

Allergic:
Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of ramipril.

In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid
exanthema and enanthema, hypersensitivity of the skin to light and onycholysis have been observed.

Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.

**Angioneurotic oedema:**
In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with ramipril must be discontinued and appropriate therapy instituted immediately.

**Respiratory tract:**
A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

**Other adverse reactions:**
Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

**Laboratory test findings:**
Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate.

Serum sodium levels may decrease. Elevation of serum potassium may occur, since ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

4.9. **Overdose**

In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

5. **PHARMACOLOGICAL PROPERTIES**

5.1. **Pharmacodynamic properties**

Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat which is a potent and long acting ACE inhibitor. 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. There is evidence suggesting that tissue ACE
particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramiprilat appears to have some effects on the kallikrein-kinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive and metabolic activity of ramipril.

Administration of ramipril to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3 - 6 hours after drug intake and has been shown to be maintained for at least 24 hours after usual therapeutic doses.

In a large endpoint study - HOPE - ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous dose-ranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the renin-angiotensin-aldosterone system. This and other studies suggest that ACE inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

5.2. Pharmacokinetic properties

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2 - 4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 - 17 hours for 5 - 10 mg ramipril and markedly longer for lower doses, 1.25 - 2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. 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.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.

5.3. Preclinical safety data
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 and higher.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Pregelatinised starch,
Gelatin,
Titanium dioxide (E171),
Azorubine (E122),
Patent blue V (E131),
Polysorbate 80 and
Sodium chloride.

6.2. Incompatibilities

None known.

6.3. Shelf life

18 months.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5. Nature and contents of container

PVC/Aclar/aluminium blister packs or HDPE bottle with polypropylene screw cap with Permaseal liner containing 7, 21 or 28 tablets.

6.6. Instruction for use and handling and disposal

None.

7. MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd.
Vision House
Bedford Road
Petersfield
Hampshire
GU32 3QB
UK.

8. MARKETING AUTHORISATION NUMBER(S)
   PL 10622/0127

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   26/06/2006

10. DATE OF REVISION OF THE TEXT
    26/06/2006
RAMIPRIL 2.5MG CAPSULES (RAMIPRIL)
PL 10622/0125

PRODUCT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET
Your prescription for Ramipril 2.5 mg Capsules

Please read this leaflet carefully before you start to use your capsules.

- This leaflet contains important information about your treatment. If you have any doubts or questions, or you are not sure about anything, ask your doctor or pharmacist.
- Keep this leaflet. You may need to read it again.
- Your medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

This leaflet contains the following information:
1. What are Ramipril 2.5 mg Capsules and what are they used for?
2. Information to read BEFORE taking Ramipril 2.5 mg Capsules.
3. How to take your medicine.
4. Can your medicine have any side-effects?
5. Storing your medicine.

The name of your medicine is Ramipril 2.5 mg Capsules. These are white and orange capsules. The active substance in your capsules is ramipril.

Other ingredients are pregelatinised starch, gelatin, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), polysorbate 80 and sodium chloride.


Manufacturers: Drakenpharm Apotheke Pöschl GmbH Co,KGm Göllstrasse 1, 84529 Tittmoning, Germany or Chandele Medical Ltd., IDA Industrial Estate, Loughrea, County Galway, Ireland

1. What are Ramipril 2.5 mg Capsules and what are they used for?

What are Ramipril 2.5 mg Capsules?
Ramipril is an Angiotensin Converting Enzyme (ACE) Inhibitor which has the effect of helping relax artery walls and removal of sodium from the body.

What are they used for?
Ramipril is used to treat patients with high blood pressure, congestive heart failure (ineffective pumping by the heart) and these symptoms following heart attack, prevention of kidney disease in diabetic patients and to reduce the risk of heart attack and stroke. It is also used to reduce the need for revascularisation procedures in patients over 55 years old who have symptoms of heart disease. Ramipril is also prescribed to patients with heart failure following a heart attack.

2. Information to read BEFORE using Ramipril 2.5 mg Capsules.
Please take the time to read the following information carefully as this may stop you from being able to take Ramipril capsules.

When should you NOT take Ramipril 2.5 mg Capsules?
Ask yourself the following questions:
- Have you ever taken a medicine containing Ramipril or any of the other ingredients listed above and had an unusual or allergic reaction?
- Do you have a history of angioneurotic oedema (fluid retention internally and under the skin)?
- Do you suffer from severe kidney problems?
- Have you had a kidney transplant?
- Do you have high sodium levels in your blood?
- Do you have low blood pressure problems?
- Are you pregnant or is there a chance you may be pregnant?
- Are you breastfeeding?
- Have the capsules been prescribed for a child?
• Do you have unstable circulation?
• Do you have narrowed heart valves or other heart obstruction?

If the answer to any of these questions is YES and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking any capsules.

**When should you take special care while taking Ramipril 2.5 mg Capsules?**

Ask yourself the following questions:

• Do you have kidney problems?
• Do you undergo regular haemodialysis?
• Are you taking allopurinol (a digestive enzyme inhibitor)?
• Are you taking immunosuppressants?
• Are you taking diuretics (‘water’ tablets) including thiazide-type or potassium sparing diuretics (e.g. spironolactone, amiloride, triamterene)?
• Are you diabetic?
• Are you taking insulin or sulphonylurea derivatives (medication to lower blood glucose levels)?
• Are you taking Non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid, indomethacin)
• Are you taking lithium?
• Are you taking corticosteroids (e.g. prednisone, dexamethasone)?
• Do you have low density lipoprotein apheresis along with dextran sulphate treatment?
• Are you taking anti-metabolites?
• Are you taking any other medication which acts on your blood?
• Do you have hyperkalaemia (high potassium levels in your blood)?
• Do you have Lupus Erythematosis, Scleroderma or other collagen vascular disease?
• Are you taking diuretics (e.g. spironolactone, amiloride or triamterene)?
• Do you have high blood pressure?
• Do you have liver problems?
• Do you have severe heart failure?
• Are you due to have surgery/anaesthetic whilst on this medication?
• Do you take medication to reduce your blood pressure?
• Are you taking adrenergic blocking medication (nerve treatment)?
• Are you taking potassium supplements?

If the answer to any of these questions is YES and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking any capsules.

It is important that you consult your doctor or pharmacist if you are taking any other medicine. If you are not sure whether another medicine you are taking may be one of the types listed above, check with your doctor or pharmacist. Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine including those that you have bought without a prescription.

**Effects on your ability to drive and use machines**

After your first dose and subsequent increases in dose it is not recommended that you drive or use machinery for several hours. Some patients may be unable to drive or use machinery whilst taking Ramipril. You may feel sleepy or dizzy after taking this medicine and that may affect your ability to drive or use machinery so care must be taken. Do not drive or use machinery if you have drunk any alcohol with this medication.

3. **How to take your capsules.**

It is important to take the capsules as directed by your doctor. Check the medicine label to see how many capsules to take and how often to take them. If you are not sure, ask your doctor or pharmacist. The capsules should be swallowed with water. Food does not affect the absorption of ramipril. Your dose will be dependent on the severity of your condition, your age and level of kidney function as well as your response to this medicine. Your doctor will choose the best dose for you.

**Adults**

*Reducing the risk of heart attack, stroke and the need for revascularisation procedures:***
The starting does is 2.5mg Ramipril once daily. The dose should be gradually increased depending on your response. The dose is usually doubled after a week and again after another 3 weeks to 10mg. This is the usual maintenance dose.

High blood pressure:
If you have not been taking any diuretics within the last few days and do not suffer from congestive heart failure (ineffective pumping by the heart) then the starting dose is 1.25mg Ramipril once a day. This may be increased at intervals of 1-2 weeks based on your response, up to a maximum dose of 10mg once daily. If your response is still unsatisfactory your doctor may give you another medicine to take in addition. If you have high blood pressure and also suffer from congestive heart failure your response should be monitored in hospital.

Congestive heart failure:
If you are stabilized on diuretic therapy your starting does is 1.25mg Ramipril once daily. This may be increased at intervals of 1-2 weeks depending on your response. The maximum dose is 10mg daily.

Following heart attack:
Your treatment of Ramipril should begin in hospital between day 3 and day 10 following your heart attack. The starting dose is 2.5mg twice daily, and is increased to 5mg twice daily after 2 days. If the initial 2.5mg dose is too much for you your doctor may give you 1.25mg twice a day for 2 days before increasing to 2.5mg and 5mg daily. If your dose cannot be increased to 2.5mg twice daily then your doctor will discontinue this medication. The usual maintenance dose is 2.5mg to 5mg twice daily.

If you are diabetic and have kidney problem:
The usual dose is 1.25mg once daily and the maximum is 5mg once daily.

Liver Problems:
The starting dose is 1.25mg once daily and your response will be closely monitored.

Elderly
Your doctor will monitor your blood pressure and will select the right dose for you.

Children
Ramipril is not recommended for use in children.

It is very important that you follow your doctors instructions as to how many Ramipril 1.25 mg Capsules to take, how often to take them and for how long you should continue to take your capsules. If you think their effect is too strong or weak, talk to your doctor, and do not change the amount you take yourself. Do not take more than you were told to. Keep taking them for as long as your doctor tells you.

If you take too many capsules
It is important to stick to the dose on the label of your medicine. If you or someone else swallows several of these capsules all together, or you think a child has swallowed any of these capsules, contact your doctor, pharmacist or hospital emergency department immediately. Always take any capsules left over with you and also the box, as this will allow easier identification of the capsules.

If you forget to take a dose
If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose though, do not take twice the number of capsules, just carry on as before.

If you start to feel better
Even when you start to feel better it is important for you to keep on taking your capsules for as long as your doctor tells you.

4. Can your capsules have any side-effects?
Like all medicines, Ramipril 2.5 mg Capsules can have side-effects.

If you suffer from any of the following side-effects, stop taking your Ramipril capsules and either tell your doctor immediately or go to your nearest hospital. You may be experiencing an allergic reaction to the capsules:

- Swelling of the hands, feet, ankles, face, lips, tongue, mouth or throat
- problems with swallowing or breathing
- Severe rash or itching

The following side-effects may occur rarely:
- Gastrointestinal effects- constipation, digestive disturbances, diarrhoea, stomach ache, feeling or being sick, upper abdominal discomfort.
- Effects on the Central Nervous System- nervousness, restlessness, shaking, problems with balance, dizziness, headache, anxiety, difficulty sleeping, loss of appetite, muscle cramps, confusion, depression, difficulty breathing, fever, muscle and joint pain, stroke, haemorrhage, fainting, tingling sensations.
- Effects on the Skin- inflammation, hot reddened areas, itching, hives, rash, hair loss, dryness, spots or blisters on skin or in mouth, sensitivity to light, discoloration or loosening of nails. Other ACE inhibitors have caused skin reactions similar to psoriasis (scaly patches of skin) or pemphigoid (fluid-filled blisters). These may also occur with ramipril.
- Respiratory System effects- irritation and inflammation of the oral lining, tickly cough, dry mouth, inflammation of the lining of the nasal passages, sinuses and lungs, wheezing.
- Effects on the Special Senses- reduction, loss or change of taste, eye infection.
- Effects on the Liver- jaundice (yellowing of the skin or eyes) which may be due to impaired excretion of bile, liver problems, increase in liver enzymes, hepatitis.
- Effects on the Pancreas- pancreatitis (inflammation of the pancreas), increase in pancreatic enzymes.
- Effects on the Kidney- impaired kidney function, pre-existing kidney damage may deteriorate.
- Effects on the Heart- rhythm disturbances, rapid heart beat, chest pain, heart attack, angina pectoris.
- Effects on the Reproductive System- inability to obtain an erection, reduction in sexual desire.
- Effects on the Blood- decreased sodium levels, increase in urea nitrogen levels, drop in blood pressure, Raynaud’s phenomenon – poor blood circulation in extremities (e.g. fingers, toes, nose), especially in the cold, increased number of some blood cells, raised antibody level, increased creatinine levels, reduced function of bone marrow, increased potassium levels, inflammation of the blood vessels.

If you suffer from any of the side-effects listed above and they are severe or prolonged or if you experience any other side-effects not mentioned on this leaflet, please inform your doctor or pharmacist immediately.

5. Storing your capsules.
Store your capsules in the original package not above 25°C and where children cannot reach or see them. Do not use this medicine after the ‘use by’ date on the carton. If you have any capsules that are out of date, return them to your pharmacist for disposal.

Remember: this treatment is for YOU. Only a doctor can prescribe it for you. Never give it to others.

Date of preparation: March 2003
RAMIPRIL 5MG & 10MG CAPSULES (RAMIPRIL)
PL 10622/0126-7

PRODUCT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Your prescription for Ramipril 5mg or 10mg Capsules

Please read this leaflet carefully before you start to use your capsules.

- This leaflet contains important information about your treatment. If you have any doubts or questions, or you are not sure about anything, ask your doctor or pharmacist.
- Keep this leaflet. You may need to read it again.
- Your medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

This leaflet contains the following information:
1. What are Ramipril Capsules and what are they used for?
2. Information to read BEFORE taking Ramipril Capsules.
3. How to take your medicine.
4. Can your medicine have any side-effects?
5. Storing your medicine.

The name of your medicine is Ramipril 5 mg Capsules or Ramipril 10 mg Capsules. Ramipril 5mg Capsules are white and red capsules. Ramipril 10mg Capsules are white and blue capsules. Ramipril 5mg Capsules contain 5mg of the active ingredient Ramipril. Other ingredients are pregelatinised starch, gelatin, titanium dioxide (E171), quinoline yellow (E104), azorubine (E122), polysorbate 80 and sodium chloride. Ramipril 10mg Capsules contain 10mg of the active ingredient Ramipril. Other ingredients are pregelatinised starch, gelatin, titanium dioxide (E171), azorubine (E122), Patent blue V (E131), polysorbate 80 and sodium chloride.

Manufacturers: Drägerpharm Apotheker Püschl GmbH Co.KG Göllstrasse 1, 84529 Tittmoning, Germany or Chanelle Medical Ltd., IDA Industrial Estate, Loughrea, County Galway, Ireland.

1. What are Ramipril Capsules and what are they used for?
What are Ramipril Capsules?
Ramipril is an Angiotensin Converting Enzyme (ACE) Inhibitor which has the effect of helping relax artery walls and removal of sodium from the body.

What are they used for?
Ramipril is used to treat patients with high blood pressure, congestive heart failure (ineffective pumping by the heart) and these symptoms following heart attack, prevention of kidney disease in diabetic patients and to reduce the risk of heart attack and stroke. It is also used to reduce the need for revascularisation procedures in patients over 55 years old who have symptoms of heart disease. Ramipril is also prescribed to patients with heart failure following a heart attack.

2. Information to read BEFORE using Ramipril Capsules.
Please take the time to read the following information carefully as this may stop you from being able to take Ramipril capsules.

When should you NOT take Ramipril Capsules?
Ask yourself the following questions:
- Have you ever taken a medicine containing Ramipril or any of the other ingredients listed above and had an unusual or allergic reaction?
- Do you have a history of angioneurotic oedema (fluid retention internally and under the skin)?
- Do you suffer from severe kidney problems?
- Do you have low blood pressure?
- Are you pregnant or is there a chance you may be pregnant?
• Are you breastfeeding?
• Have the capsules been prescribed for a child?
• Do you have unstable circulation?
• Do you have narrowed heart valves or other heart obstruction?

If the answer to any of these questions is YES and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking any capsules.

When should you take special care while taking Ramipril Capsules?
Ask yourself the following questions:
• Do you have kidney problems?
• Do you undergo regular haemodialysis?
• Have you had a kidney transplant?
• Are you diabetic?
• Do you have hyperkalaemia (high potassium levels in your blood?)
• Do you have high sodium levels in your blood?
• Do you have Lupus Erythematosus, Scleroderma or other collagen vascular disease?

• Do you have high blood pressure?
• Do you have liver problems?
• Do you have severe heart failure or congestive heart failure?
• Are you due to have surgery/anesthetic whilst on this medication?
• Do you take medication to reduce your blood pressure?

If the answer to any of these questions is YES and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking any capsules.

Are you taking any of the following medicines:
• Are you taking allopurinol (a digestive enzyme inhibitor)?
• Are you taking diuretics (‘water’ tablets) including thiazide-type or potassium sparing diuretics (e.g. spironolactone, amiloride, triamterene)?
• Are you taking insulin or sulphonylurea derivatives (medication to lower blood glucose levels)?
• Are you taking Non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid, indomethacin)
• Are you taking lithium?
• Are you taking corticosteroids (e.g. prednisone, dexamethasone)?
• Do you have low density lipoprotein apheresis along with dextran sulphate treatment?
• Are you taking anti-metabolites?
• Are you taking any other medication which acts on your blood?
• Are you taking adrenergic blocking medication (nerve treatment)?
• Are you taking potassium supplements?
• Are you taking immunosuppressants?

It is important that you consult your doctor or pharmacist if you are taking any other medicine. If you are not sure whether another medicine you are taking may be one of the types listed above, check with your doctor or pharmacist. Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine including those that you have bought without a prescription.

These capsules contain E122 (azorubine) which may cause allergic reactions.

Effects on your ability to drive and use machines
After your first dose and subsequent increases in dose it is not recommended that you drive or use machinery for several hours. Some patients may be unable to drive or use machinery whilst taking Ramipril. You may feel sleepy or dizzy after taking this medicine and that may affect your ability to drive or use machinery so care must be taken. Do not drive or use machinery if you have drunk any alcohol with this medication.
3. **How to take your capsules.**

It is important to take the capsules as directed by your doctor. Check the medicine label to see how many capsules to take and how often to take them. If you are not sure, ask your doctor or pharmacist. The capsules should be swallowed with water. Food does not affect the absorption of ramipril. Your dose will be dependent on the severity of your condition, your age and level of kidney function as well as your response to this medicine. Your doctor will choose the best dose for you.

**Adults**

*Reducing the risk of heart attack, stroke and the need for revascularisation procedures:*

The starting does is 2.5mg Ramipril once daily. The dose should be gradually increased depending on your response. The dose is usually doubled after a week and again after another 3 weeks to 10mg. This is the usual maintenance dose.

*High blood pressure:*

If you have not been taking any diuretics within the last few days and do not suffer from congestive heart failure (ineffective pumping by the heart) then the starting dose is 1.25mg Ramipril once a day. This may be increased at intervals of 1-2 weeks based on your response, up to a maximum dose of 10mg once daily. If you have high blood pressure and also suffer from congestive heart failure your response should be monitored in hospital.

*Congestive heart failure:*

If you are stabilised on diuretic therapy your starting dose is 1.25mg Ramipril once daily. This may be increased at intervals of 1-2 weeks depending on your response. The maximum dose is 10mg daily.

*Following heart attack:*

Your treatment of Ramipril should begin in hospital between day 3 and day 10 following your heart attack. The starting dose is 2.5mg twice daily, and is increased to 5mg twice daily after 2 days. If the initial 2.5mg dose is too much for you your doctor may give you 1.25mg twice a day for 2 days before increasing to 2.5mg and 5mg daily. If your dose cannot be increased to 2.5mg twice daily then your doctor will discontinue this medication. The usual maintenance dose is 2.5mg to 5mg twice daily.

*If you have kidney problems:*

The usual dose is 1.25mg once daily and the maximum is 5mg once daily. The maximum dose for patients with severe kidney problems is 2.5mg once daily.

*Liver Problems:*

The starting dose is 1.25mg once daily and your response will be closely monitored.

*Elderly*

Your doctor will monitor your blood pressure and will select the right dose for you.

*Children*

Ramipril is not recommended for use in children.

It is very important that you follow your doctors instructions as to how many Ramipril 5 Capsules to take, how often to take them and for how long you should continue to take your capsules. If you think their effect is too strong or weak, talk to your doctor, and do not change the amount you take yourself. Do not take more than you were told to. Keep taking them for as long as your doctor tells you.

*If you take too many capsules*

It is important to stick to the dose on the label of your medicine. However if you or someone else swallows several of these capsules all together, or you think a child has swallowed any of these capsules, contact your doctor, pharmacist or hospital emergency department immediately. Always take any capsules left over with you and also the box, as this will allow easier identification of the capsules.

*If you forget to take a dose*

If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose though, do not take twice the number of capsules, just carry on as before.

*If you start to feel better*

Even when you start to feel better it is important for you to keep taking your capsules for as long as your doctor tells you.

4. **Can your capsules have any side-effects?**

Like all medicines, Ramipril Capsules can have side-effects.
If you suffer from any of the following side-effects, stop taking your Ramipril capsules and either tell your doctor immediately or go to your nearest hospital. You may be experiencing an allergic reaction to the capsules.

- Swelling of the hands, feet, ankles, face, lips, tongue, mouth or throat
- problems with swallowing or breathing.
- Severe rash or itching

The following side-effects may occur:

- Gastrointestinal effects - constipation, digestive disturbances, diarrhoea, stomach ache, feeling or being sick, upper abdominal discomfort.
- Effects on the Central Nervous System - weakness, nervousness, restlessness, shaking, problems with balance, dizziness, headache, anxiety, difficulty sleeping, loss of appetite, muscle cramps, confusion, depression, fever, muscle and joint pain, stroke, fainting, tingling sensations or pins and needles.
- Effects on the Skin - hot reddened areas, itching, hives, rash, hair loss, spots or blisters on skin, in mouth or other mucous membranes.

Other ACE inhibitors have caused skin reactions similar to psoriasis (scaly patches of skin) or pemphigoid (fluid-filled blisters), sensitivity to light, discoloration or loosening of nails. These may also occur with ramipril.

- Respiratory System effects - difficulty breathing, irritation and inflammation of the oral lining, tickly cough, dry mouth, inflammation of the lining of the nasal passages, sinuses and lungs, wheezing.

- Effects on the Special Senses - reduction, loss or change of taste, eye infection.
- Effects on the Liver - jaundice (yellowing of the skin or eyes) which may be due to impaired excretion of bile, liver problems, increase in liver enzymes, hepatitis.
- Effects on the Pancreas - pancreatitis (inflammation of the pancreas), increase in pancreatic enzymes.
- Effects on the Kidney - impaired kidney function, pre-existing kidney damage may deteriorate, an increase of protein levels in the blood.
- Effects on the Heart - rapid heart beat, chest pain, heart attack, angina pectoris.
- Effects on the Reproductive System - inability to obtain an erection, reduction in sexual desire.
- Effects on the Blood - decreased sodium levels, increase in urea nitrogen levels, drop in blood pressure, Raynaud’s phenomenon – poor blood circulation in extremities (e.g., fingers, toes, nose), especially in the cold, changes in the number of some blood cells, raised antibody level, increased creatinine levels, bone marrow depression, increased potassium levels, decreased sodium levels, inflammation of the blood vessels.

If you suffer from any of the side-effects listed above and they are severe or prolonged or if you experience any other side-effects not mentioned on this leaflet, please inform your doctor or pharmacist immediately.

5. Storing your capsules.

Store your capsules in the original package not above 25°C and where children cannot reach or see them. Do not use this medicine after the ‘use by’ date on the carton. If you have any capsules that are out of date, return them to your pharmacist for disposal.

*Remember: this treatment is for YOU. Only a doctor can prescribe it for you. Never give it to others.*

Date of preparation: March 2005
RAMIPRIL 2.5MG CAPSULES (RAMIPRIL)
PL 10622/0125

LABELLING

BOTTLE CARTON

BLISTER PACK CARTON
RAMIPRIL 5MG CAPSULES (RAMIPRIL)
PL 10622/0126

LABELLING

BOTTLE CARTON

BLISTER PACK CARTON