

Ramipril 1.25 mg Capsules
PL 17907/0228

Ramipril 2.5 mg Capsules
PL 17907/0229

Ramipril 5mg Capsules
PL 17907/0230

Ramipril 10mg Capsules
PL 17907/0231

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Ramipril 1.25 mg Capsules
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Ramipril 2.5 mg Capsules
PL 17907/0229

Ramipril 5mg Capsules
PL 17907/0230

Ramipril 10mg Capsules
PL 17907/0231

LAY SUMMARY

The MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Ramipril 1.25 mg Capsules (PL 17907/0228), Ramipril 2.5 mg Capsules (PL 17907/0229), Ramipril 5mg Capsules (PL 17907/0230), and Ramipril 10mg Capsules (PL 17907/0231) on 2nd July 2007. These prescription only medicines (POM) are indicated for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients over the age of 55 years.

Ramipril capsules contain the active ingredient ramipril. Ramipril belongs to a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors, which act on heart and blood vessels.

These applications are duplicates of previously granted applications for Ramipril 1.25mg Capsules, Ramipril 2.5mg Capsules, Ramipril 5mg Capsules, and Ramipril 10mg Capsules which had, in turn, demonstrated essential similarity or equivalence to the approved product, Ramipril 1.25mg Capsules, Ramipril 2.5 mg Capsules, Ramipril 5mg Capsules and Ramipril 10mg Capsules, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Ramipril 1.25mg Capsules, Ramipril 2.5mg Capsules, Ramipril 5mg Capsules, and Ramipril 10mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.

**Ramipril 1.25 mg Capsules
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PL 17907/0230**

**Ramipril 10mg Capsules
PL 17907/0231**

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Ramipril 1.25 mg Capsules (PL 17907/0228), Ramipril 2.5 mg Capsules (PL 17907/0229), Ramipril 5mg Capsules (PL 17907/0230), and Ramipril 10mg Capsules (PL 17907/0231) to Bristol Laboratories Limited on 2nd July 2007. The products are prescription only medicines.

The applications were submitted as simple abridged applications according to article 10.1(c) of Directive 2001/83/EC as amended, cross-referring to Ramipril 1.25mg Capsules, Ramipril 2.5 mg Capsules, Ramipril 5mg Capsules and Ramipril 10mg Capsules (PL 17907/0063-6), approved on 7th September 2005.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PARs were generated for them.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 17907/0228-31

PROPRIETARY NAME: Ramipril 1.25 mg capsules, Ramipril 2.5 mg Capsules, Ramipril 5mg Capsules, and Ramipril 10mg Capsules

ACTIVE(S): ramipril

COMPANY NAME: Bristol Laboratories Limited

E.C. ARTICLE: Article 10 (c) of Directive 2001/83/EC as amended

LEGAL STATUS: POM

1. INTRODUCTION

This is a simple, piggy back application for Ramipril 1.25 mg capsules, 2.5 mg Capsules, 5 mg Capsules, and 10 mg Capsules submitted under Article 10 (c) of Directive 2001/83/EC as amended. The proposed MA holder is “Bristol Laboratories Limited, UNIT 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG”.

These applications cross refer to the marketing authorisations held by Bristol Laboratories Ltd (PL 17907/0063-6) and a suitable letter of access to the data has been provided by them (letter dated 23/05/2006). This was acceptable.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference products and that there are no toxicological or clinical issues.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

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

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain ramipril equivalent to 1.25 mg, 2.5 mg, 5 mg and 10 mg of ramipril respectively. They are to be stored in transparent aluminium/PVC/PVDC blister packs. Each blister contains 14 capsules which are placed in an outer carton containing 2 blister strips. The blisters are constructed of PVDC coated PVC and aluminium foil. The proposed shelf-life (2 years) and storage conditions (Do not store above 25°C; Store in the original package) are consistent with the details registered for the cross-reference products.

2.3 Legal status

On approval, the products are subject to a medical prescription.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Bristol Laboratories Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire, HP4 1EG, United Kingdom.

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

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference products.

2.9 Drug substance specification

The proposed drug substance specification conformed to current Ph Eur monograph for ramipril and was consistent with that of the reference product.

2.10 TSE Compliance

Gelatin was declared in Section 2.6.2 of the MAA form. Current versions of TSE CEP certificates for gelatin have been provided and the applicant has supplied a letter confirming that the product complies with the CHMP TSE requirements.

3. EXPERT REPORTS

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

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/BLISTER

PIL

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

Carton / Blister

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

7. CONCLUSIONS

The data submitted with the applications are acceptable. Marketing Authorisations should be granted.

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

As these are duplicate applications for PL 17907/0063-6, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

Ramipril is a well known drug and has been used for many years. These applications are identical to previously granted applications for Ramipril capsules (PL 17907/0063-6).

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference products and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products. Extensive clinical experience with ramipril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 09/06/2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 11/08/2006.
3	Following assessment of the application the MHRA requested further information on 24/08/2006, 28/03/2007 and 02/05/2007.
4	The applicant responded to the MHRA's requests, providing further information on 27/03/2007, 30/03/2007, and 14/05/2007
5	The application was determined on 02/07/2007

Ramipril 1.25 mg Capsules
PL 17907/0228

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 1.25 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Ramipril 1.25 mg

Excipients: carmoisine (E122)

Sunset yellow (E110)

Ponceau 4R (E124)

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

For a full list of excipients, see section 6. 1

3 PHARMACEUTICAL FORM

Capsule, Hard

Yellow/white coloured gelatin capsules of size "4"

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ramipril Capsules are indicated for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients over the age of 55 years:

- Who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.
- Who are diabetic and 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.

Ramipril Capsules are also indicated for the treatment of essential hypertension.

Ramipril Capsules have 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

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

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5mg of 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 of ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg of ramipril once daily.

Hypertension: The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25mg to 2.5mg of ramipril once a day. The dose should be increased incrementally at intervals of 1-2 weeks. This should be based on patient response, up to a maximum of 10mg once a day.

A 1.25mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5-5mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10mg of 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 1.25mg under close medical supervision in hospital.

Post myocardial infarction: Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI the starting dose is 2.5mg twice a day which is increased to 5mg twice a day after 2 days. If the initial 2.5mg dose is not tolerated a dose of 1.25mg twice a day should be given for two days before increasing to 2.5mg and 5.0mg twice a day. If the dose cannot be increased to 2.5mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5mg twice a day.

Dose adjustment in renal impairment: In patients with impaired renal function (creatinine clearance between 20 and 50 ml/min/1.73 m²) 1.25 mg ramipril is recommended as the initial dose, while the maximum daily dose must not be more than 5 mg ramipril once daily.

In patients with a creatinine clearance < 20 ml/min/1.73 m², 1.25 mg ramipril every second day is recommended as the initial dose, while the maximum daily dose must not be more than 2.5 mg ramipril once daily.

Dose 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 diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25mg 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 Capsules have not been studied in this patient group, and therefore use is not recommended.

4.3 Contraindications

- Hypersensitivity to ramipril, any of the excipients or other ACE inhibitors
- A history of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see section 4.6)
- Haemodynamically relevant renal artery stenosis (both sides) or unilateral stenosis in the single kidney
- Lactation

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving ramipril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given

usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with ramipril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of ramipril may be necessary.

Hypotension in acute myocardial infarction

Treatment with ramipril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, ramipril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy. In haemodynamically relevant cases ramipril should not be administered

Renal function impairment

In cases of renal impairment (creatinine clearance ≤ 30 ml/min), the initial ramipril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of ramipril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ramipril may be required.

In acute myocardial infarction, treatment with ramipril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with ramipril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of ramipril.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including ramipril. This may occur at any time during therapy. In such cases, ramipril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti hypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

Patients with hepatic impairment may have an impaired capacity to form the active metabolite ramiprilat. There is not enough experience to give definite dose recommendations. Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/ Agranulocytosis

Neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Ramipril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If ramipril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce 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 volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including ramipril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5.)

Lithium

The combination of lithium and ramipril is generally not recommended (see section 4.5.).

4.5 Interaction with other medicinal products and other forms of interaction

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of ramipril. Particularly close blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of haematological reactions (see also under “4.4 Special Warnings and Special Precautions for use”).

Lithium Salts: Excretion of lithium may be reduced by ACE inhibitors, Such reduction may lead to increased serum lithium levels and increased lithium toxicity. Lithium levels must, therefore, be monitored.

Diuretics and other antihypertensive agents: Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril, 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. Regular monitoring of serum sodium and potassium is recommended in patients undergoing concurrent diuretic therapy. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Combination with antidiabetics: When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered. Particularly close blood glucose monitoring is therefore recommended in the initial phase of co-administration.

Combination with NSAIDs: When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indometacin), attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium.

Heparin: Rise in serum potassium concentration possible.

Desensitisation therapy: The likelihood and severity of anaphylactic and phylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

4.6 Pregnancy and lactation

Pregnancy

Ramipril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. The exposure limited to first trimester of pregnancy may be associated with the increased risk of congenital malformation of cardiovascular and central nervous system.

Ramipril is contraindicated during the second and third trimester of pregnancy (see section 4.3).

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3).

Should exposure to ramipril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken ramipril should be closely monitored for hypotension, oliguria and hyperkalaemia. ACE inhibitors, which cross the placenta, have been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether ramipril is excreted into human breast milk. Ramipril is excreted into the milk of lactating rats. The use of ramipril is contraindicated during breast-feeding

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

The following undesirable effects have been observed during treatment with ramipril and other ACE inhibitors with the following frequencies: Very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), very rare ($< 1/10,000$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.
very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, agranulocytosis (see section 4.4.), haemolytic anaemia, lymphadenopathy, autoimmune disease

These changes in blood picture occur more often in patients with renal insufficiency and in patients with a vascular collagen disease, such as lupus erythematosus and scleroderma, and in simultaneous use of medicines that may also instigate changes in blood picture (see sections 4.4 and 4.5).

Metabolism and nutrition disorders

very rare: hypoglycaemia

Nervous system and psychiatric disorders:

common: dizziness, headache
uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
rare: mental confusion

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)
uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

common: cough
uncommon: dyspnoea, rhinitis
very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:

common: diarrhoea, vomiting

- uncommon: nausea, abdominal pain and indigestion, anorexia
rare: dry mouth
very rare: pancreatitis, hepatitis- either hepatocellular or cholestatic, jaundice, intestinal angioedema.

Skin and subcutaneous tissue disorders:

- uncommon: rash, pruritus
rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see section 4.4), urticaria, alopecia, psoriasis
very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:

- common: renal dysfunction
rare: uraemia, acute renal failure
very rare: oliguria/anuria

Reproductive system and breast disorders:

- uncommon: impotence
rare: gynaecomastia

General disorders and administration site conditions:

- uncommon: fatigue, asthenia

Investigations:

- uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
rare: increases in serum bilirubin, hyponatraemia.

4.9 Overdose

Symptoms

Over dosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Management

In the event of prolonged hypotension, administration of “alpha1- adrenergic agonists” (e.g. norepinephrine, dopamine) and angiotensin II (angiotensinamide) must be considered in addition to volume and salt substitution.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C09AA05

Pharmacotherapeutic group: ACE inhibitor

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 10 mg 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

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

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

Capsule contents:

Pregelatinised maize starch

Capsule shell:

Gelatin

Ferric oxide yellow (E 172)

Titanium dioxide (E171)

Sodium Laurilsulfate

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blisters of 14 capsules: packaged into an outer carton to give a pack size of 28 capsules.

6.6 Special precautions for disposal

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited

Unit 3, Canalside

Northbridge Road

Berkhamsted

Herts, HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0228

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/07/2007

10 DATE OF REVISION OF THE TEXT

02/07/2007

Ramipril 2.5 mg Capsules
PL 17907/0229

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 2.5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Ramipril 2.5 mg

Excipients: carmoisine (E122)

Sunset yellow (E110)

Ponceau 4R (E124)

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

For a full list of excipients, see section 6. 1

3 PHARMACEUTICAL FORM

Capsule, hard

Orange/white coloured gelatin capsules of size “4”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ramipril Capsules are indicated for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients over the age of 55 years:

- Who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.
- Who are diabetic and 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.

Ramipril Capsules are also indicated for the treatment of essential hypertension.

Ramipril Capsules have 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

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

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5mg of 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 of ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg of ramipril once daily.

Hypertension: The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25mg to 2.5mg of ramipril once a day. The dose should be increased incrementally at intervals of 1-2 weeks. This should be based on patient response, up to a maximum of 10mg once a day.

A 1.25mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5-5mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10mg of 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 1.25mg under close medical supervision in hospital.

Post myocardial infarction: Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI the starting dose is 2.5mg twice a day which is increased to 5mg twice a day after 2 days. If the initial 2.5mg dose is not tolerated a dose of 1.25mg twice a day should be given for two days before increasing to 2.5mg and 5.0mg twice a day. If the dose cannot be increased to 2.5mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5mg twice a day.

Dose adjustment in renal impairment: In patients with impaired renal function (creatinine clearance between 20 and 50 ml/min/1.73 m²) 1.25 mg ramipril is recommended as the initial dose, while the maximum daily dose must not be more than 5 mg ramipril once daily.

In patients with a creatinine clearance < 20 ml/min/1.73 m², 1.25 mg ramipril every second day is recommended as the initial dose, while the maximum daily dose must not be more than 2.5 mg ramipril once daily.

Dose 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 diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25mg 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 Capsules have not been studied in this patient group, and therefore use is not recommended.

4.3 Contraindications

- Hypersensitivity to ramipril, any of the excipients or other ACE inhibitors
- A history of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see section 4.6)
- Haemodynamically relevant renal artery stenosis (both sides) or unilateral stenosis in the single kidney
- Lactation

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving ramipril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with ramipril. This effect is

anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of ramipril may be necessary.

Hypotension in acute myocardial infarction

Treatment with ramipril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, ramipril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy. In haemodynamically relevant cases ramipril should not be administered

Renal function impairment

In cases of renal impairment (creatinine clearance \leq 30 ml/min), the initial ramipril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of ramipril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ramipril may be required.

In acute myocardial infarction, treatment with ramipril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with ramipril (serum creatinine concentration

exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of ramipril.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including ramipril. This may occur at any time during therapy. In such cases, ramipril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis Patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti hypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

Patients with hepatic impairment may have an impaired capacity to form the active metabolite ramiprilat. There is not enough experience to give definite dose recommendations. Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/ Agranulocytosis

Neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Ramipril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If ramipril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce 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 volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including ramipril. Patients at risk for the development of hyperkalaemia

include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5.)

Lithium

The combination of lithium and ramipril is generally not recommended (see section 4.5.).

Ramipril 2.5mg Capsules contain the colourants ponceau 4R (E124) and sunset yellow (E110), which can cause allergic type reactions including asthma. Allergy is more common in patients who are allergic to aspirin

4.5 Interaction with other medicinal products and other forms of interaction

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of ramipril. Particularly close blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of haematological reactions (see also under “4.4 Special Warnings and Special Precautions for use”).

Lithium Salts: Excretion of lithium may be reduced by ACE inhibitors, such reduction may lead to increased serum lithium levels and increased lithium toxicity. Lithium levels must, therefore, be monitored.

Diuretics and other antihypertensive agents: Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril, 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. Regular monitoring of serum sodium and potassium is recommended in patients undergoing concurrent diuretic therapy. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Combination with antidiabetics: When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered. Particularly close blood glucose monitoring is therefore recommended in the initial phase of co-administration.

Combination with NSAIDs: When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indometacin), attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of

ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium.

Heparin: Rise in serum potassium concentration possible.

Desensitisation therapy: The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

4.6 Pregnancy and lactation

Pregnancy

Ramipril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. The exposure limited to first trimester of pregnancy may be associated with the increased risk of congenital malformation of cardiovascular and central nervous system.

Ramipril is contraindicated during the second and third trimester of pregnancy (see section 4.3).

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3).

Should exposure to ramipril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken ramipril should be closely monitored for hypotension, oliguria and hyperkalaemia. ACE inhibitors, which cross the placenta, have been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether ramipril is excreted into human breast milk. Ramipril is excreted into the milk of lactating rats. The use of ramipril is contraindicated during breast-feeding.

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

The following undesirable effects have been observed during treatment with ramipril and other ACE inhibitors with the following frequencies: Very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), very rare ($< 1/10,000$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.
very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, agranulocytosis (see section 4.4.), haemolytic anaemia, lymphadenopathy, autoimmune disease

These changes in blood picture occur more often in patients with renal insufficiency and in patients with a vascular collagen disease, such as lupus erythematosus and scleroderma, and in simultaneous use of medicines that may also instigate changes in blood picture (see sections 4.4 and 4.5).

Metabolism and nutrition disorders

very rare: hypoglycaemia

Nervous system and psychiatric disorders:

common: dizziness, headache
uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
rare: mental confusion

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)
uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

common: cough
uncommon: dyspnoea, rhinitis
very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:

common: diarrhoea, vomiting
uncommon: nausea, abdominal pain and indigestion, anorexia

- rare: dry mouth
- very rare: pancreatitis, hepatitis- either hepatocellular or cholestatic, jaundice, intestinal angioedema.

Skin and subcutaneous tissue disorders:

- uncommon: rash, pruritus
- rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see section 4.4), urticaria, alopecia, psoriasis
- very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:

- common: renal dysfunction
- rare: uraemia, acute renal failure
- very rare: oliguria/anuria

Reproductive system and breast disorders:

- uncommon: impotence
- rare: gynaecomastia

General disorders and administration site conditions:

- uncommon: fatigue, asthenia

Investigations:

- uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
- rare: increases in serum bilirubin, hyponatraemia.

4.9 Overdose

Symptoms

Over dosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Management

In the event of prolonged hypotension, administration of “alpha1- adrenergic agonists” (e.g. norepinephrine, dopamine) and angiotensin II (angiotensinamide) must be considered in addition to volume and salt substitution.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C09AA05

Pharmacotherapeutic group: ACE inhibitor

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 10 mg 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

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

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

Capsule contents:

Pregelatinised maize starch

Capsule shell:

Gelatin

Sunset yellow (E 110)

Ponceau 4 R (E124)

Carmoisine (E 122)

Titanium dioxide (E171)

Sodium Laurilsulfate

Methyl Hydroxybenzoate (E218)

Propyl hydroxybenzoate (E216)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blisters of 14 capsules: packaged into an outer carton to give a pack size of 28 capsules.

6.6 Special precautions for disposal

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited

Unit 3, Canalside

Northbridge Road

Berkhamsted

Herts, HP4 IEG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0229

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/07/2007

10 DATE OF REVISION OF THE TEXT

02/07/2007

Ramipril 5 mg Capsules
PL 17907/0230

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Ramipril 5 mg

Excipients: carmoisine (E122)

Ponceau 4R (E124)

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

For a full list of excipients, see section 6. 1

3 PHARMACEUTICAL FORM

Capsule, hard

Maroon/white coloured gelatin capsules of size “4”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ramipril Capsules are indicated for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients over the age of 55 years:

- Who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.
- Who are diabetic and 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.

Ramipril Capsules are also indicated for the treatment of essential hypertension.

Ramipril Capsules have 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

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

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5mg of 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 of ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg of ramipril once daily.

Hypertension: The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25mg to 2.5mg of ramipril once a day. The dose should be increased incrementally at intervals of 1-2 weeks. This should be based on patient response, up to a maximum of 10mg once a day.

A 1.25mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5-5mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10mg of 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 1.25mg under close medical supervision in hospital.

Post myocardial infarction: Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI the starting dose is 2.5mg twice a day which is increased to 5mg twice a day after 2 days. If the initial 2.5mg dose is not tolerated a dose of 1.25mg twice a day should be given for two days before increasing to 2.5mg and 5.0mg twice a day. If the dose cannot be increased to 2.5mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5mg twice a day.

Dose adjustment in renal impairment: In patients with impaired renal function (creatinine clearance between 20 and 50 ml/min/1.73 m²) 1.25 mg ramipril is recommended as the initial dose, while the maximum daily dose must not be more than 5 mg ramipril once daily.

In patients with a creatinine clearance < 20 ml/min/1.73 m², 1.25 mg ramipril every second day is recommended as the initial dose, while the maximum daily dose must not be more than 2.5 mg ramipril once daily.

Dose 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 diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25mg 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 Capsules have not been studied in this patient group, and therefore use is not recommended.

4.3 Contraindications

- Hypersensitivity to ramipril, any of the excipients or other ACE inhibitors
- A history of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see section 4.6)
- Haemodynamically relevant renal artery stenosis (both sides) or unilateral stenosis in the single kidney
- Lactation

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving ramipril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with ramipril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of ramipril may be necessary.

Hypotension in acute myocardial infarction

Treatment with ramipril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a

vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, ramipril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy. In haemodynamically relevant cases ramipril should not be administered

Renal function impairment

In cases of renal impairment (creatinine clearance ≤ 30 ml/min), the initial ramipril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of ramipril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ramipril may be required.

In acute myocardial infarction, treatment with ramipril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with ramipril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of ramipril.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including ramipril. This may occur at any time during therapy. In such cases, ramipril

should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti hypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

Patients with hepatic impairment may have an impaired capacity to form the active metabolite ramiprilat. There is not enough experience to give definite dose recommendations. Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic

enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/ Agranulocytosis

Neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Ramipril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If ramipril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce 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 volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including ramipril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5.)

Lithium

The combination of lithium and ramipril is generally not recommended (see section 4.5.).

Ramipril 5mg Capsules contain the colourants carmoisine (E122), ponceau 4R (E124) and Brilliant blue (E133), which can cause allergic type reactions including asthma. Allergy is more common in patients who are allergic to aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of ramipril. Particularly close blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of haematological reactions (see also under “4.4 Special Warnings and Special Precautions for use”).

Lithium Salts: Excretion of lithium may be reduced by ACE inhibitors, such reduction may lead to increased serum lithium levels and increased lithium toxicity. Lithium levels must, therefore, be monitored.

Diuretics and other antihypertensive agents: Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril, 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. Regular monitoring of serum sodium and potassium is recommended in patients undergoing concurrent diuretic therapy. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Combination with antidiabetics: When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered. Particularly close blood glucose monitoring is therefore recommended in the initial phase of co-administration.

Combination with NSAIDs: When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indometacin), attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium.

Heparin: Rise in serum potassium concentration possible.

Desensitisation therapy: The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

4.6 Pregnancy and lactation

Pregnancy

Ramipril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. The exposure limited to first trimester of pregnancy may be associated with the increased risk of congenital malformation of cardiovascular and central nervous system.

Ramipril is contraindicated during the second and third trimester of pregnancy (see section 4.3).

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3).

Should exposure to ramipril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken ramipril should be closely monitored for hypotension, oliguria and hyperkalaemia. ACE inhibitors, which cross the placenta, have been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether ramipril is excreted into human breast milk. Ramipril is excreted into the milk of lactating rats. The use of ramipril is contraindicated during breast-feeding

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

The following undesirable effects have been observed during treatment with ramipril and other ACE inhibitors with the following frequencies: Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, agranulocytosis (see section 4.4.), haemolytic anaemia, lymphadenopathy, autoimmune disease

These changes in blood picture occur more often in patients with renal insufficiency and in patients with a vascular collagen disease, such as lupus erythematosus and scleroderma, and in simultaneous use of medicines that may also instigate changes in blood picture (see sections 4.4 and 4.5).

Metabolism and nutrition disorders

very rare: hypoglycaemia

Nervous system and psychiatric disorders:

common: dizziness, headache

uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.

rare: mental confusion

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)

uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

common: cough

uncommon: dyspnoea, rhinitis

very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:

common: diarrhoea, vomiting

uncommon: nausea, abdominal pain and indigestion, anorexia

rare: dry mouth

very rare: pancreatitis, hepatitis- either hepatocellular or cholestatic, jaundice, intestinal angioedema.

Skin and subcutaneous tissue disorders:

uncommon: rash, pruritus

rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see section 4.4), urticaria, alopecia, psoriasis

very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:

common: renal dysfunction
rare: uraemia, acute renal failure
very rare: oliguria/anuria

Reproductive system and breast disorders:

uncommon: impotence
rare gynaecomastia

General disorders and administration site conditions:

uncommon: fatigue, asthenia

Investigations:

uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
rare: increases in serum bilirubin, hyponatraemia.

4.9 Overdose

Symptoms

Over dosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Management

In the event of prolonged hypotension, administration of “alpha1- adrenergic agonists” (e.g. norepinephrine, dopamine) and angiotensin II (angiotensinamide) must be considered in addition to volume and salt substitution.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C09AA05

Pharmacotherapeutic group: ACE inhibitor

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 10 mg 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

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

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****Capsule contents:**

Pregelatinised maize starch

Capsule shell:

Gelatin

Ponceau 4 R (E124)

Brilliant blue (E 133)

Carmoisine (E 122)

Titanium dioxide (E171)

Sodium Laurilsulfate

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blisters of 14 capsules: packaged into an outer carton to give a pack size of 28 capsules.

6.6 Special precautions for disposal

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited

Unit 3, Canalside

Northbridge Road

Berkhamsted

Herts, HP4 IEG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0230

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

02/07/2007

10 DATE OF REVISION OF THE TEXT

02/07/2007

Ramipril 10 mg Capsules
PL 17907/0231

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 10 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Ramipril 10 mg

Excipients: carmoisine (E122)

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

For a full list of excipients, see section 6. 1

3 PHARMACEUTICAL FORM

Capsule, hard

Blue/white coloured gelatin capsules of size “4”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ramipril Capsules are indicated for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients over the age of 55 years:

- Who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.
- Who are diabetic and 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.

Ramipril Capsules are also indicated for the treatment of essential hypertension.

Ramipril Capsules have 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

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

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5mg of 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 of ramipril once a day. Patients already stabilised on lower doses of ramipril for other indications where possible should be titrated to 10mg of ramipril once daily.

Hypertension: The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25mg to 2.5mg of ramipril once a day. The dose should be increased incrementally at intervals of 1-2 weeks. This should be based on patient response, up to a maximum of 10mg once a day.

A 1.25mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5-5mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10mg of 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 1.25mg under close medical supervision in hospital.

Post myocardial infarction: Initiation of therapy: Treatment must be started in hospital between day 3 and day 10 following AMI the starting dose is 2.5mg twice a day which is increased to 5mg twice a day after 2 days. If the initial 2.5mg dose is not tolerated a dose of 1.25mg twice a day should be given for two days before increasing to 2.5mg and 5.0mg twice a day. If the dose cannot be increased to 2.5mg twice a day treatment should be withdrawn.

Maintenance dose: 2.5 to 5mg twice a day.

Dose adjustment in renal impairment: In patients with impaired renal function (creatinine clearance between 20 and 50 ml/min/1.73 m²) 1.25 mg ramipril is recommended as the initial dose, while the maximum daily dose must not be more than 5 mg ramipril once daily.

In patients with a creatinine clearance < 20 ml/min/1.73 m², 1.25 mg ramipril every second day is recommended as the initial dose, while the maximum daily dose must not be more than 2.5 mg ramipril once daily.

Dose 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 diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25mg 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 Capsules have not been studied in this patient group, and therefore use is not recommended.

4.3 Contraindications

- Hypersensitivity to ramipril, any of the excipients or other ACE inhibitors
- A history of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see section 4.6)
- Haemodynamically relevant renal artery stenosis (both sides) or unilateral stenosis in the single kidney
- Lactation

4.4 Special warnings and precautions for use

Symptomatic hypotension

Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving ramipril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with ramipril. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension

becomes symptomatic, a reduction of dose or discontinuation of ramipril may be necessary.

Hypotension in acute myocardial infarction

Treatment with ramipril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100 mm Hg or lower or those in cardiogenic shock.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

As with other ACE inhibitors, ramipril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy. In haemodynamically relevant cases ramipril should not be administered

Renal function impairment

In cases of renal impairment (creatinine clearance \leq 30 ml/min), the initial ramipril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of ramipril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ramipril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or ramipril may be required.

In acute myocardial infarction, treatment with ramipril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with ramipril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of ramipril.

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including ramipril. This may occur at any time during therapy. In such cases, ramipril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of anti hypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Hepatic failure

Patients with hepatic impairment may have an impaired capacity to form the active metabolite ramiprilat. There is not enough experience to give definite dose recommendations. Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/ Agranulocytosis

Neutropenia/ agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Ramipril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If ramipril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Race

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce 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 volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including ramipril. Patients at risk for the development of hyperkalaemia

include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5.)

Lithium

The combination of lithium and ramipril is generally not recommended (see section 4.5.).

Ramipril 10mg Capsules contain the colourant carmoisine (E122), Brilliant blue (E133) and erythrosine (E127) which can cause allergic type reactions including asthma. Allergy is more common in patients who are allergic to aspirin. Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of ramipril. Particularly close blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: Increased likelihood of haematological reactions (see also under “4.4 Special Warnings and Special Precautions for use”).

Lithium Salts: Excretion of lithium may be reduced by ACE inhibitors, such reduction may lead to increased serum lithium levels and increased lithium toxicity. Lithium levels must, therefore, be monitored.

Diuretics and other antihypertensive agents: Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to ramipril, 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. Regular monitoring of serum sodium and potassium is recommended in patients undergoing concurrent diuretic therapy. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Combination with antidiabetics: When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction

must be considered. Particularly close blood glucose monitoring is therefore recommended in the initial phase of co-administration.

Combination with NSAIDs: When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indometacin), attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium.

Heparin: Rise in serum potassium concentration possible.

Desensitisation therapy: The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom is increased under ACE inhibition. It is assumed that this effect may also occur in connection with other allergens.

4.6 Pregnancy and lactation

Pregnancy

Ramipril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed, the switch to an alternative treatment should be initiated as soon as possible. The exposure limited to first trimester of pregnancy may be associated with the increased risk of congenital malformation of cardiovascular and central nervous system.

Ramipril is contraindicated during the second and third trimester of pregnancy (see section 4.3).

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3).

Should exposure to ramipril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken ramipril should be closely monitored for hypotension, oliguria and hyperkalaemia. ACE inhibitors, which cross the placenta, have been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

It is not known whether ramipril is excreted into human breast milk. Ramipril is excreted into the milk of lactating rats. The use of ramipril is contraindicated during breast-feeding.

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

The following undesirable effects have been observed during treatment with ramipril and other ACE inhibitors with the following frequencies: Very common ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$), rare ($\geq 1/10,000, < 1/1,000$), very rare ($< 1/10,000$) including isolated reports.

Blood and the lymphatic system disorders:

rare: decreases in haemoglobin, decreases in haematocrit.
very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, agranulocytosis (see section 4.4.), haemolytic anaemia, lymphadenopathy, autoimmune disease

These changes in blood picture occur more often in patients with renal insufficiency and in patients with a vascular collagen disease, such as lupus erythematoses and sclerodermia, and in simultaneous use of medicines that may also instigate changes in blood picture (see sections 4.4 and 4.5).

Metabolism and nutrition disorders

very rare: hypoglycaemia

Nervous system and psychiatric disorders:

common: dizziness, headache
uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
rare: mental confusion

Cardiac and vascular disorders:

common: orthostatic effects (including hypotension)
uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

common: cough
uncommon: dyspnoea, rhinitis
very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:

- common: diarrhoea, vomiting
- uncommon: nausea, abdominal pain and indigestion, anorexia
- rare: dry mouth
- very rare: pancreatitis, hepatitis- either hepatocellular or cholestatic, jaundice, intestinal angioedema.

Skin and subcutaneous tissue disorders:

- uncommon: rash, pruritus
- rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see section 4.4), urticaria, alopecia, psoriasis
- very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:

- common: renal dysfunction
- rare: uraemia, acute renal failure
- very rare: oliguria/anuria

Reproductive system and breast disorders:

- uncommon: impotence
- rare: gynaecomastia

General disorders and administration site conditions:

- uncommon: fatigue, asthenia

Investigations:

- uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
- rare: increases in serum bilirubin, hyponatraemia.

4.9 Overdose

Symptoms

Over dosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

Management

In the event of prolonged hypotension, administration of “alpha1- adrenergic agonists” (e.g. norepinephrine, dopamine) and angiotensin II (angiotensinamide) must be considered in addition to volume and salt substitution.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C09AA05

Pharmacotherapeutic group: ACE inhibitor

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 10 mg 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

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

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

Capsule contents:

Pregelatinised maize starch

Capsule shell:

Gelatin

Brilliant blue (E133)

Carmoisine (E 122)

Erythrosine (E127)

Titanium dioxide (E171)

Sodium Laurilsulfate

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC/PVDC blisters of 14 capsules: packaged into an outer carton to give a pack size of 28 capsules.

6.6 Special precautions for disposal

No special requirements

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted
Herts, HP4 1EG

8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0231

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/07/2007

10 DATE OF REVISION OF THE TEXT

02/07/2007

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ramipril 1.25mgCapsules/
 Ramipril 2.5mgCapsules/
 Ramipril 5mg Capsules/
 Ramipril 10mg Capsules

Active Substance: Ramipril

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions or are unsure please ask your doctor or pharmacist.
- This 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.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ramipril Capsules are and what they are used for
2. Before you take Ramipril Capsules
3. How to take Ramipril Capsules
4. Possible side effects
5. How to store Ramipril Capsules
6. Further Information

1. What Ramipril Capsules are What they are Used for

Ramipril capsules contain the active ingredient Ramipril. Ramipril belongs to a group of medicines called Angiotensin Converting Enzyme (ACE) inhibitors, which act on heart and blood vessels.

Ramipril Capsules are prescribed to you for one or more of the following reasons:

- to lower your blood pressure if it is high.
- to prevent your heart from weakening further if you have had a heart attack.
- in patients who are 55 years or older and suffer from heart and circulation problems, or who have previously had a stroke, Ramipril Capsules may be prescribed to reduce the risk of a heart attack, stroke, further heart or circulatory problems or to lessen the need for a surgical procedure to increase the blood flow to the heart.

2. Before you take Ramipril Capsules**Do not take Ramipril Capsules if you:**

- have previously suffered from the hypersensitivity reaction angioneurotic oedema (a sudden swelling of the skin or airways (e.g. throat or tongue) and/or itching and rash) without any apparent cause or after previous use of a medicine that belongs to the group of ACE-inhibitors
- have had hypersensitivity reactions (angioneurotic oedema) occur in your family .
- are pregnant or breastfeeding
- have problems with the blood supply to your kidneys.
- are allergic (hypersensitive) to Ramipril or any ingredients listed in Section 6, Further Information.

Take special care with this medicine if you:

- have any heart valve problems, such as blockages or murmurs, as Ramipril may not be suitable.
- have kidney problems, so that your doctor can assess your kidney problem and if necessary adjust your dose of Ramipril Capsules.
- have liver problems, as your doctor may want to monitor you closely.
- are on haemodialysis.
- have lupus erythematosus (chronic inflammation) or scleroderma (a disease that can cause thickening, hardening, or tightening of the skin, blood vessels and internal organs).
- are dehydrated or suffering from salt reduction, for example as a result of excessive sweating, diarrhoea, or vomiting.
- are having desensitisation therapy(treatment to build up your immunity to an allergen).
- need surgery or an anaesthetic.
- are to undergo Low-density lipoproteins (LDL) apheresis (in which the blood of a donor or patient is passed through an apparatus that separates out one particular constituent and returns the remainder to the circulation)

Ask your doctor or pharmacist if you have any doubt.

Taking other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, but bought by you, especially any of the following:

- nonsteroidal anti-inflammatory drugs (e.g. aspirin, ibuprofen or indometacin),
- diuretics (water tablets), for example spironolactone, amiloride, triamterene, bendroflumethiazide or furosemide,

- medicines for high blood pressure or heart disease, such as beta-blockers (e.g. propranolol or atenolol), calcium-channel blockers (e.g. nifedipine or diltiazem), or alpha-blockers (e.g. doxazosin),
- medicines for diabetes (such as insulin, glibenclamide or gliclazide),
- anti-coagulants (e.g. heparin),
- lithium, (used in the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorder (manic-depressive disorder) and recurrent depression)
- treatment for gout (e.g. allopurinol),
- corticosteroids (e.g. prednisolone),
- drugs to depress the immune system (e.g. ciclosporin),
- procainamide (used to treat an irregular heartbeat),
- medicines containing potassium (e.g. potassium chloride),
- certain drugs used to treat cancer.

Ask your doctor or pharmacist if you have any doubt

Pregnancy and breast-feeding:

- You should not take Ramipril Capsules if you are pregnant or breast-feeding.
- Tell your doctor as soon as possible if you think you have become pregnant whilst taking Ramipril Capsules or if you intend to become pregnant.
- Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:

- Ramipril Capsules may cause dizziness or tiredness, especially when you first start taking them.
- We recommend that you do not drive or operate machinery for several hours after taking Ramipril Capsules for the first time or if you are increasing your dose of Ramipril Capsules.
- Drinking alcohol may also make these symptoms worse. If this happens to you, do not drive or use machinery.

Important information about some of the ingredients of Ramipril Capsules

- **Ramipril capsules contain methyl hydroxy benzoate and propyl hydroxy benzoate which may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm.**
- **The 2.5mg, 5mg and 10mg capsules also contain the colour carmoisine (E122) which may cause allergic reactions**
- **The 2.5mg & 5mg capsules contain the colour ponceau 4R (E124) which may cause allergic reactions**
- **The 2.5mg capsules contain the colour sunset yellow (E110) which may cause allergic reactions**

Although Ramipril Capsules contain a very small amount of these, if you have been told by your doctor that you are allergic to these ingredients, contact your doctor or pharmacist before taking this medicine.

3. How to take Ramipril Capsules

- Take the capsules exactly as directed by your doctor. If you do not understand these instructions, ask your doctor or pharmacist or nurse to explain them to you. The usual doses are detailed below. You should always follow your doctor's instructions as to how and when to take your medicines.
- Ramipril Capsules should be swallowed with a drink of water. If you have trouble swallowing the capsule, tell your doctor. Ramipril Capsules are not affected by food therefore can be taken before or after meals.
- For treating high blood pressure, the usual start dose is 1.25mg to 2.5mg once a day. Your doctor may increase the dose after one or two weeks of the treatment.
- In most cases of hypertension (high blood pressure), a dose of 2.5mg or 5mg is required once a day, but your doctor may increase the dose up to a maximum of 10mg per day.
- For treating congestive heart failure, the usual starting dose is 1.25mg per day, although your doctor may increase the dose after one or two weeks of treatment. In most cases a dose of 2.5mg or 5mg is required once a day, but your doctor may increase the dose up to a maximum of 10mg per day.
- Following a heart attack the usual starting dose is 2.5mg twice a day, which may be increased to 5mg twice a day after a few days, or in some cases, the dose may be reduced to 1.25mg twice a day.
- To reduce the risk of heart attack, stroke and the need for surgery to improve the blood flow to your heart, the usual starting dose is 2.5mg once a day. However, the dose may be increased to 5mg after 1 week and then up to 10mg once a day after another 3 weeks.
- If you are elderly, taking diuretics (water tablets), or have kidney or liver problems, your doctor may start you with a low dose, and increase the dose if needed.

Ramipril Capsules are not recommended for children. Ask your doctor or pharmacist if you have any doubt.

If you take more Ramipril Capsules than you should:

If you take more capsules than you should or if you take the wrong strength of Ramipril Capsules, tell your doctor immediately or go to the nearest hospital A&E (casualty) department.

If you forget to take Ramipril Capsules:

If you miss a dose, take the missed dose as soon as possible, and then continue with your normal course. If it is almost time for you to take the next dose, skip the missed dose and then take your next dose when it is due. Do not take a double dose to make up the missed dose.

If you stop taking Ramipril Capsules:

Do not stop taking Ramipril without first talking to your doctor. If you stop taking this medication, your condition could become worse.

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

4. Possible Side Effects

Like all medicines, Ramipril Capsules can cause unwanted effects, although not everybody gets them.

These are generally mild and transient, not requiring therapy to be discontinued.

Side effects can occur during treatment with Ramipril with the following frequencies:

- very common (probably affecting more than 1 in 10 patients);
- common (probably affecting more than 1 in 100, but less than 1 in 10 patients);
- uncommon (probably affecting more than 1 in 1,000, but less than 1 in 100 patients);
- rare (probably affecting more than 1 in 10,000, but less than 1 in 1,000 patients);
- very rare (probably affecting less than 1 in 10,000 patients)

The following side effects have been reported:

Effects on blood and lymphatic system:

- Rare: decreases in haemoglobin, decreases in haematocrit (erythrocytes in the blood)
- Very rare: bone marrow depression, anaemia, thrombocytopenia (few platelets in blood), leucopenia (decreased total number of white blood cells), agranulocytosis (acute reduction in the number of white blood cells), haemolytic anaemia, lymphadenopathy (swelling of one or more lymph nodes/glands), autoimmune disease.

Effects on the heart and circulation:

- Common: dizziness, headache, low blood pressure
- Uncommon: heart attack or damage to blood vessels in the brain, palpitations, rapid beating of the heart, Raynaud's phenomenon, (attacks of pain, numbness, coldness and blueness of the fingers)

Effects on airways or breathing:

- Common: cough
- Uncommon: shortness of breath, rhinitis (irritation of eyes, nose & throat)
- Very rare: difficulty in breathing, sinusitis (inflammation of sinus), allergic alveolitis (inflammation in the lungs).

Effects on digestive system:

- Common: diarrhoea, vomiting
- Uncommon: nausea (feeling sick), abdominal pain, indigestion, anorexia (eating disorder leading to extreme weight loss)
- Rare: dry mouth
- Very rare: yellowing of the skin or eyes due to obstructed bile flow (cholestatic jaundice) or liver damage (hepatitis), intestinal angiodema, pancreatitis

Effects on the skin:

- Uncommon: rash, pruritus (itching)
- Rare: hypersensitivity reaction, angioneurotic oedema (sudden swelling of the skin or airways e.g. face, extremities, lips, throat or tongue and/or itching and rash) without any apparent cause or after previous use of a

medicine that belongs to the group of ACE-inhibitors, urticaria (allergic reaction that causes raised red skin), alopecia (hair loss), psoriasis

- Very rare: diaphoresis (excessive sweating), pemphigus (autoimmune disorder), toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme (inflammatory skin eruption)

Effects on the kidneys:

- Common: impaired renal function.
- Rare: Uraemia (accumulation of urea in blood), acute renal failure
- Very rare: oliguria/anuria (little or no production of urine)

Effect on nervous system:

- Common: dizziness, headache
- Uncommon: mood alterations, paraesthesia (pins and needles sensation), vertigo, taste disturbance, sleep disturbances
- Rare: mental confusion

Effect on metabolism:

- Very rare: hypoglycaemia

Effect on reproductive system

- Uncommon: impotence
- Rare: gynecomastia (development of abnormally large breasts on men)

Other Side effects:

- Uncommon: fatigue, asthenia (feeling of weakness), increases in serum creatinine, liver enzymes, hyperkalemia (increased potassium levels in blood)
- Rare: increase in serum bilirubin, hyponatraemia (decrease in sodium levels)

STOP TAKING THE TABLETS IMMEDIATELY AND GO TO YOUR DOCTOR OR THE NEAREST A&E (casualty) department if:

- Your breathing becomes difficult and noisy.
- You get swelling of tongue, face or throat.
- You feel ill after your first dose and feel dizzy, weak, faint and sick.
- You get lot of infections with sore throats or mouth ulcers.
- You notice a rash, skin eruption or other effects on the skin or eyes, itching or a high temperature.

These are all very serious side effects and are rare. If you have these or you may have had a serious allergic reaction to Ramipril Capsules, you may need urgent medical attention or hospitalisation

- **If you notice any of the above side effects or any unusual or unexpected side effects that are not listed in this leaflet after taking Ramipril Capsules, please inform your doctor or pharmacist.**

5. How to Store Ramipril Capsules

- Keep out of the reach and sight of children.
- Do not use the capsules after the expiry date shown on the carton.
- Do not store above 25°C. Store in the original blister pack.

6. Further Information**What Ramipril capsules contain**

- The active substance in Ramipril Capsules is Ramipril.
- The other ingredient of the powder in Ramipril capsules is pregelatinised maize starch.
- The capsule shell for all strengths of Ramipril capsules contains gelatin, titanium dioxide (E171), sodium laurilsulfate, methyl parahydroxy benzoate and propyl parahydroxy benzoate.
- In addition the capsule shell for
 - Ramipril 1.25mg capsules contains the colours yellow ferric oxide (E172).
 - Ramipril 2.5mg capsules contain the colours sunset yellow (E110), ponceau 4R (E124), and carmoisine (E122).
 - Ramipril 5mg capsules contain the colours ponceau 4R (E124), brilliant blue (E133) and carmoisine (E122)
 - Ramipril 10mg capsules contain the colours brilliant blue (E133), erythrosine (E127), carmoisine (E122)

What Ramipril capsules look like and contents of the pack

Ramipril 1.25mg Capsules are yellow and white capsules.

Ramipril 2.5mg Capsules are orange and white capsules.

Ramipril 5mg Capsules are maroon and white capsules.

Ramipril 10mg Capsules are blue and white capsules.

Ramipril Capsules are available in packs containing 28 capsules.

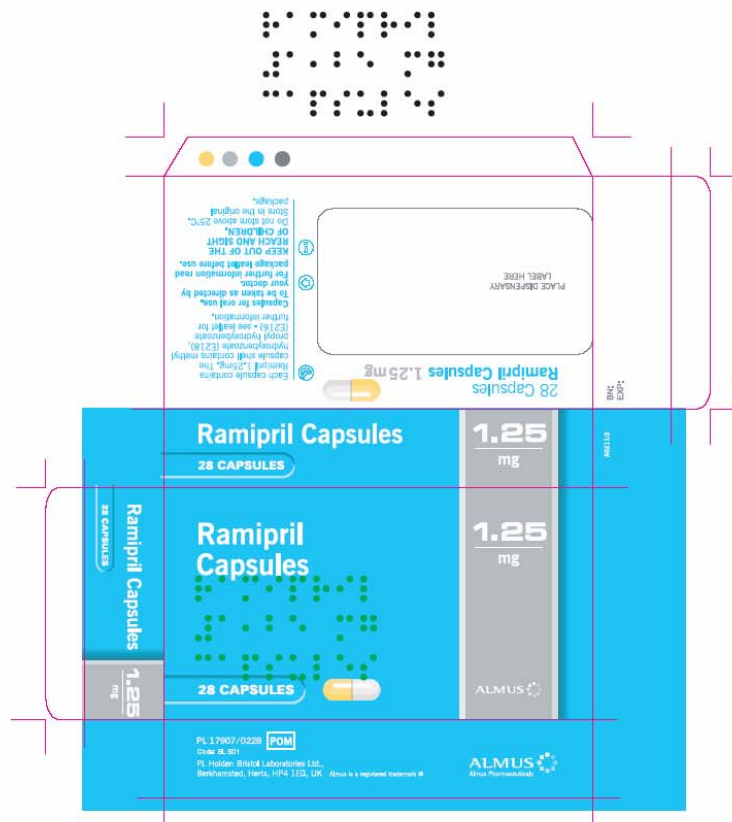
In Poland this product is marketed as

- RAMVE 1.25mg
- RAMVE 2.5mg
- RAMVE 5mg
- RAMVE 10mg

Marketing Authorization Holder and Manufacturer:

Bristol Laboratories Limited, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG, United Kingdom.

This leaflet was last approved in April 2007.



MHRA APPROVED
VERSION: 2
MHRA APPROVAL DATE: TBC
SUPPLIER ISSUE DATE: 23.6.2006

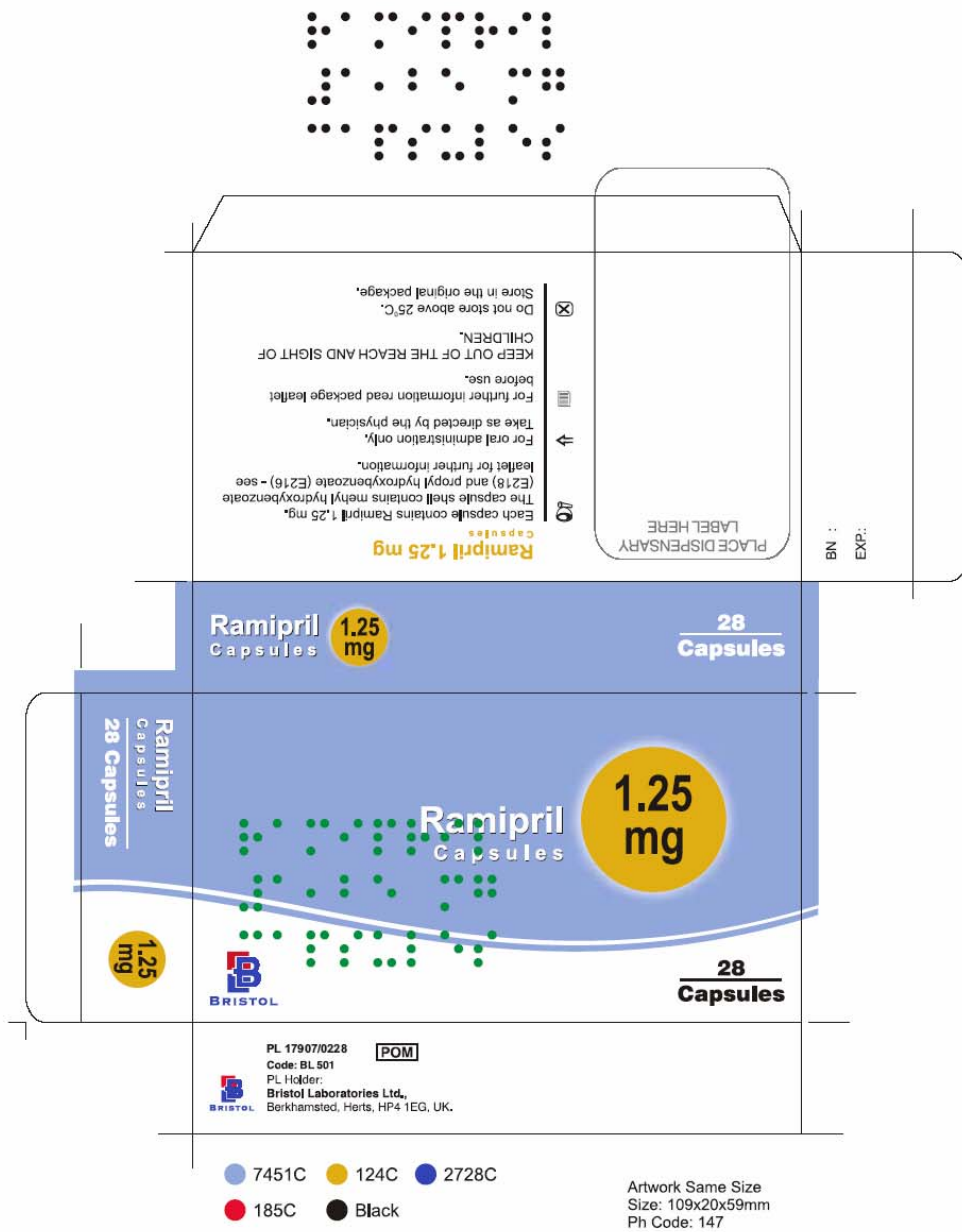
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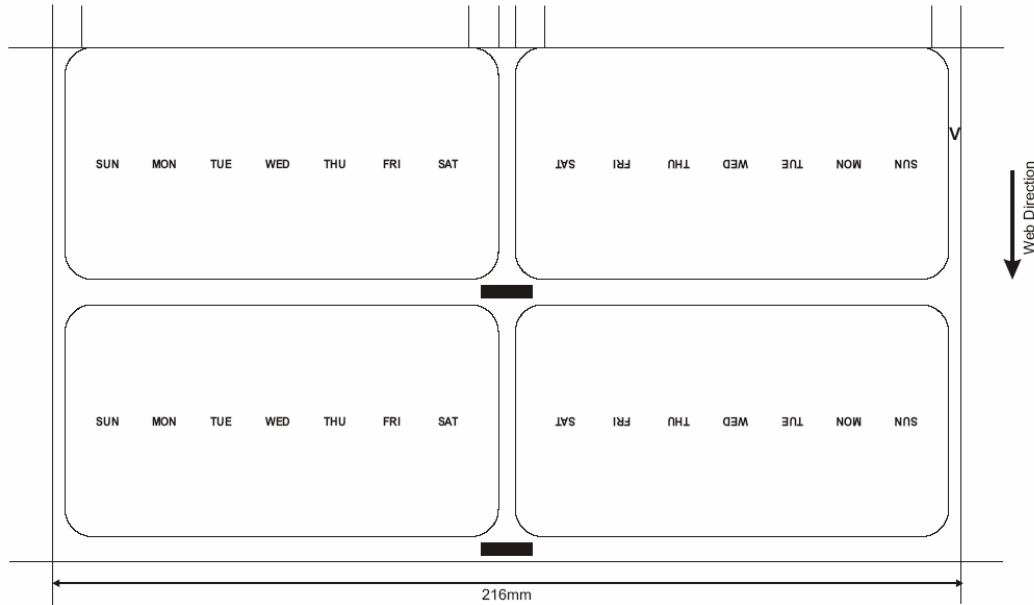
ipca ipca Laboratories Ltd. <small>Regd. Off.: 40, Kandivli Ind. Estate, Mumbai 400 067</small>	
PRODUCT	Ramipril 1.25 Capsules Carton 28's
DIMENSIONS	109 x 20 x 59 mm
FLAP WIDTH	10 mm
PANTON NOS.	Pan 424 C Pan 299 C Pan 6401 C Pan 134 C
MATERIAL	
ARTIST SIGN	POC SIGN
DATE	DATE

Graphic Creations

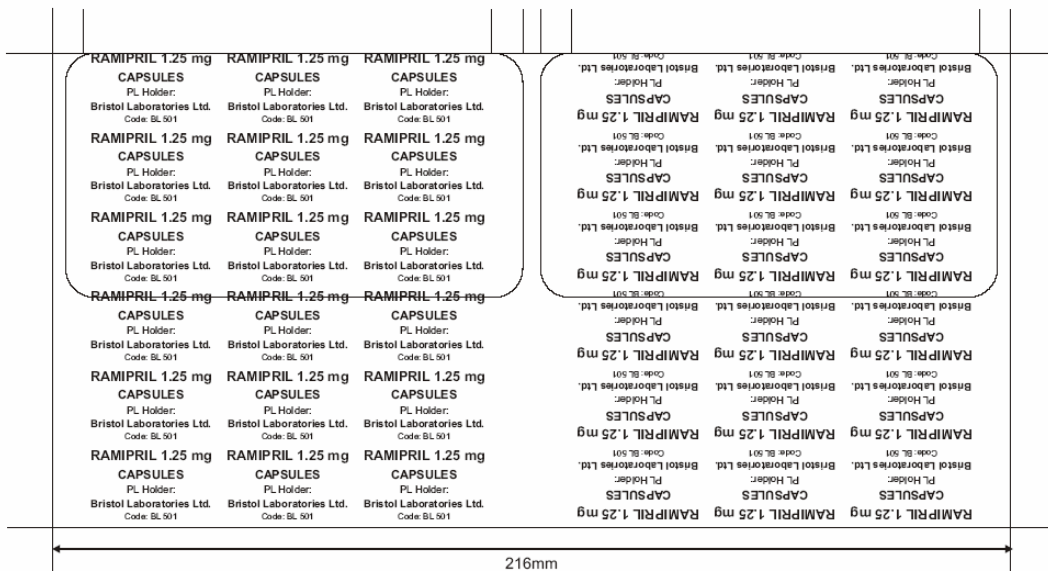
PLEASE NOTE: LASER COPIES ARE SUPPLIED AS A VISUAL REFERENCE ONLY. DO NOT MATCH FOR COLOUR

<p>ARTWORK SPECIFICATION</p> <p>Client: OTC Direct</p> <p>Project: 4477 / A / UK Almus Version 2 Products</p> <p>Item(s): Ramipril 1.25mg carton artwork</p> <p>Software: Adobe Illustrator 10.0</p>	<p>Fonts: Text outlined</p> <p>Please Note: Occasional conversion of Adobe Illustrator files to final file in movement of text. Therefore, artwork and proof(s) must be checked by printer and client against designers proof(s) accompanying this artwork. Colours may also require adjustment for 'tag' and 'overprint' to printer's own specifications.</p>	<p>Special Colours:</p> <p>PMS 04 PMS 299 PMS 6401 PMS 134</p> <p>GUTTER</p>	<p>Checked by: Steve Hobbs</p> <p>Queries regarding this artwork, please contact: Steve Hobbs or Paul Adams</p> <p>Date: 6.2.2006</p> <p>Special Instructions: Cutter shown as Special Colour 'GUTTER', do not print.</p>	<p>22 Dragon Street Peterfield Hampshire GU21 4JJ</p> <p>tel +44 (0)1730 268814 fax +44 (0)1730 263014 e-mail mail@pmdc.co.uk</p> <p style="text-align: center;"></p> <p style="text-align: center;">The Paul Martin Design Company</p>
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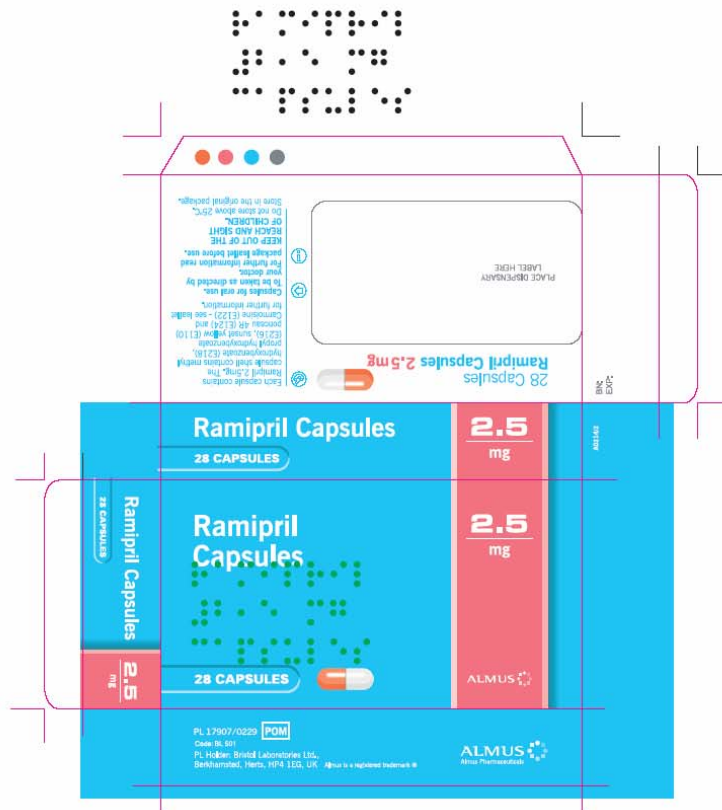




Black
 Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61.2 (Length 61.2x10=612-611.5)
 Common Bottom foil for Ramipril 1.25/2.5/5&10
 Graphic Creations



Black
 Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61.2 (Length 61.2x10=612-611.5)
 Graphic Creations



MHRA APPROVED
VERSION: 2
MHRA APPROVAL DATE: TBC
SUPPLIER ISSUE DATE: 23.6.2006

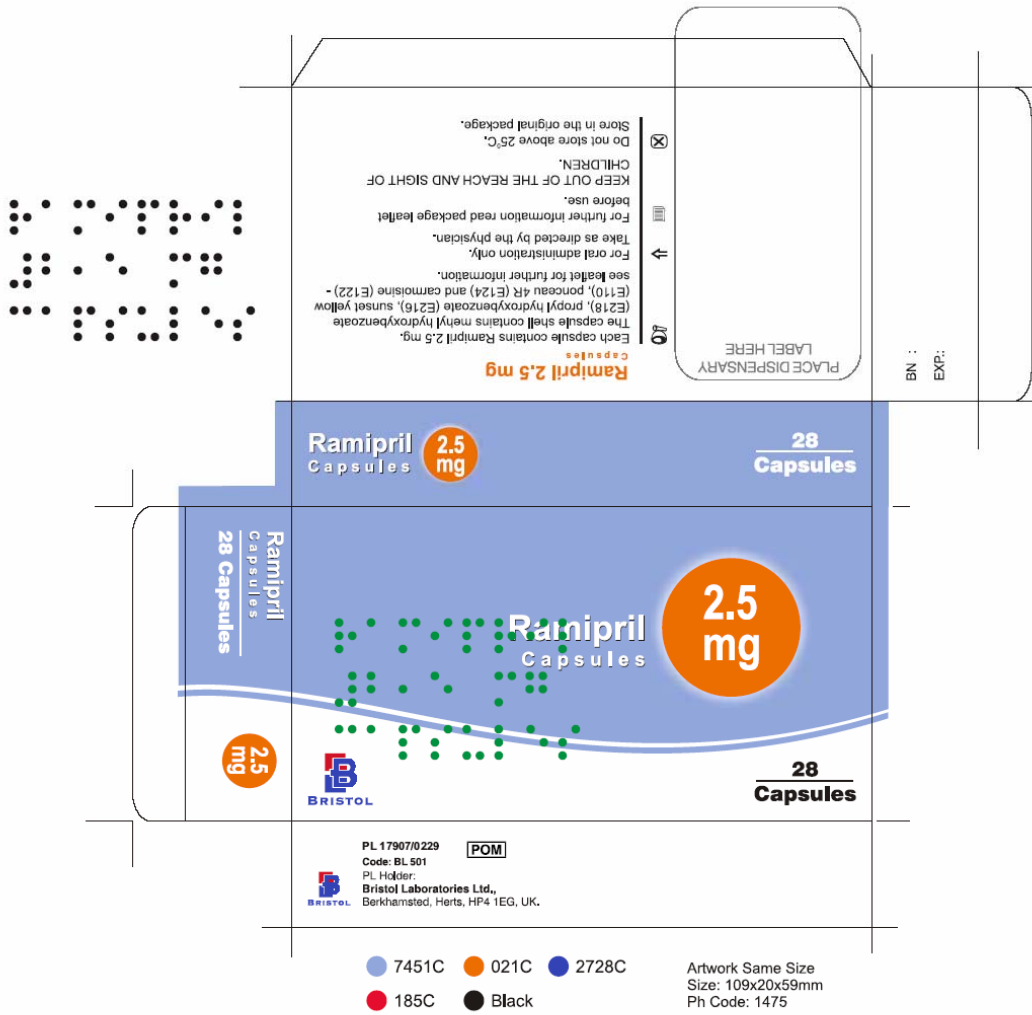
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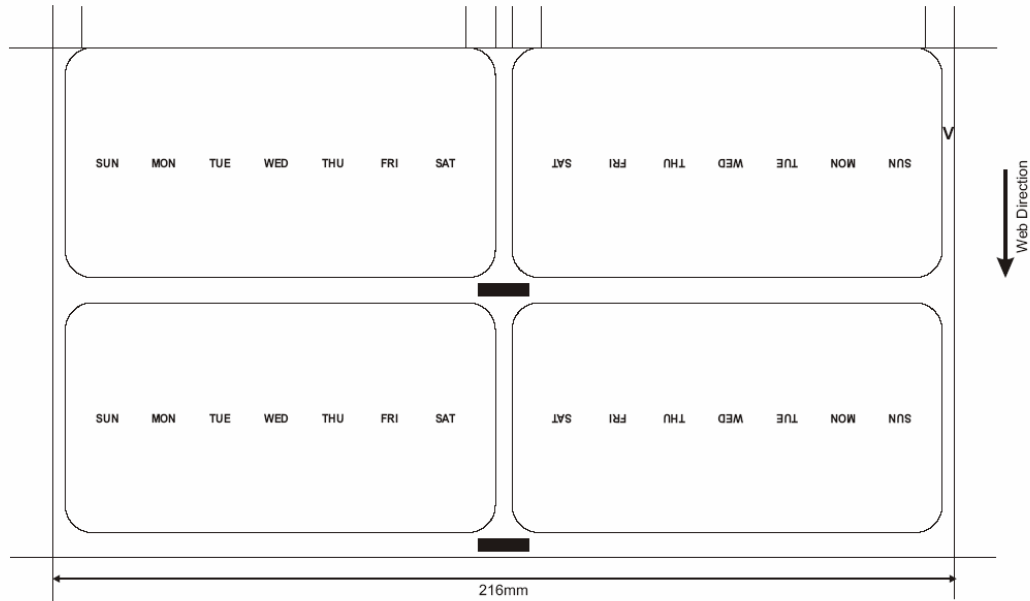
ipca Laboratories Ltd. Regd. Off: 45, Wancholi Ind. Estate, Mumbai 400 067	
PRODUCT	Ramipril 2.5 Capsules Carton 28's
DIMENSIONS	109 x 20 x 59 mm
FLAP WIDTH	10 mm
PANTON NOS.	Pan 424 C Pan 299 C Pan 702 C Pan 1645 C
MATERIAL	
ARTIST SIGN	PDC SIGN
DATE	DATE

Graphic Creations

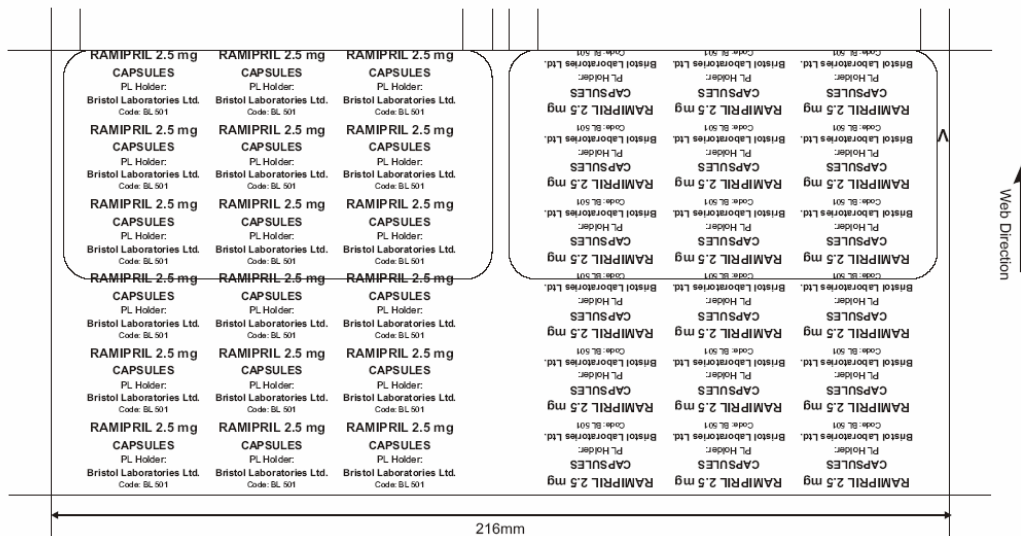
PLEASE NOTE: LASER COPIES ARE SUPPLIED AS A VISUAL REFERENCE ONLY. DO NOT MATCH FOR COLOUR

<p>ARTWORK SPECIFICATION</p> <p>Client: OTC Direct</p> <p>Project: 4477 / A / UK Almus Version 2 Products</p> <p>Item(s): Ramipril 2.5mg carton artwork</p> <p>Software: Adobe Illustrator 10.0</p>	<p>Fonts: Text outlined</p> <p>Special Colours:</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="background-color: #4a7c9c; width: 15px; height: 15px; margin-right: 5px;"></div> PMS 424 <div style="background-color: #e67e22; width: 15px; height: 15px; margin-right: 5px;"></div> PMS 299 <div style="background-color: #e91e63; width: 15px; height: 15px; margin-right: 5px;"></div> PMS 702 <div style="background-color: #f39c12; width: 15px; height: 15px; margin-right: 5px;"></div> PMS 1645</div> <p style="text-align: center; margin-top: 5px;"> CUTTER</p> <p>Please Note: Occasionally conversion of Adobe Illustrator files to final film can result in movement of text. Therefore, artwork and proof(s) must be checked by printer and client against designers proof(s) accompanying this artwork. Colours may also require adjustment for 'trap' and 'overprint' to printer's own specifications.</p>	<p>Checked by: Steve Hobbs</p> <p>Queries regarding this artwork, please contact: Steve Hobbs or Paul Adams</p> <p>Date: 6.2.2006</p> <p>Special Instructions: Cutter shown as Special Colour 'CUTTER', do not print.</p>	<p>32 Dragon Street Petersfield Hampshire GU31 4JY</p> <p>tel +44 (0)1730 265814 fax +44 (0)1730 265014 e-mail mail@pmdc.co.uk</p> <div style="text-align: right; margin-top: 20px;"> The Paul Martin Design Company </div>
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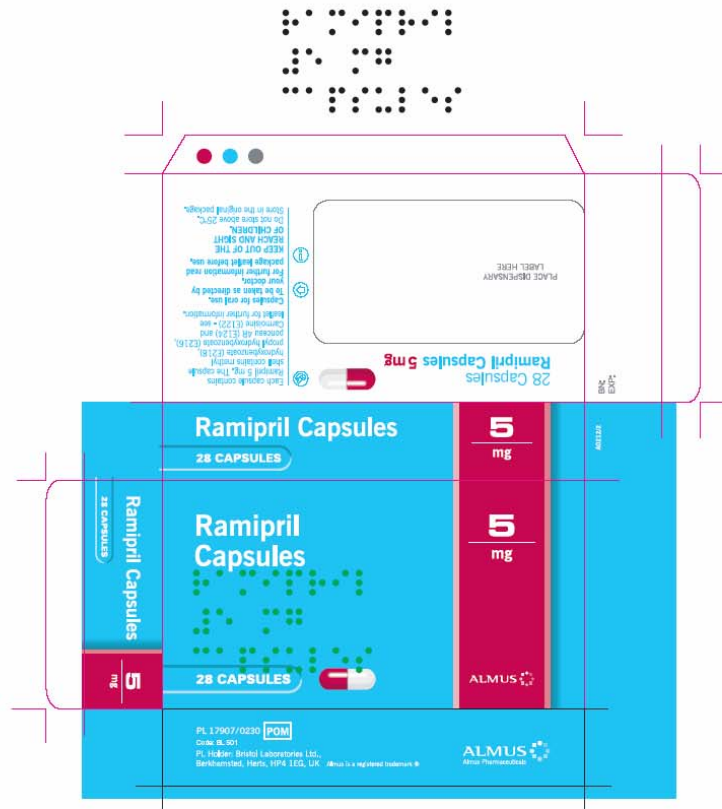




Black
 Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61.2 (Length 61.2x10=612-611.5)
 Common Bottom foil for Ramipril 1.25/2.5/5&10
 Graphic Creations



Black
 Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61.2 (Length 61.2x10=612-611.5)
 Graphic Creations




MHRA APPROVED
VERSION: 2
MHRA APPROVAL DATE: TBC
SUPPLIER ISSUE DATE: 23.6.2006

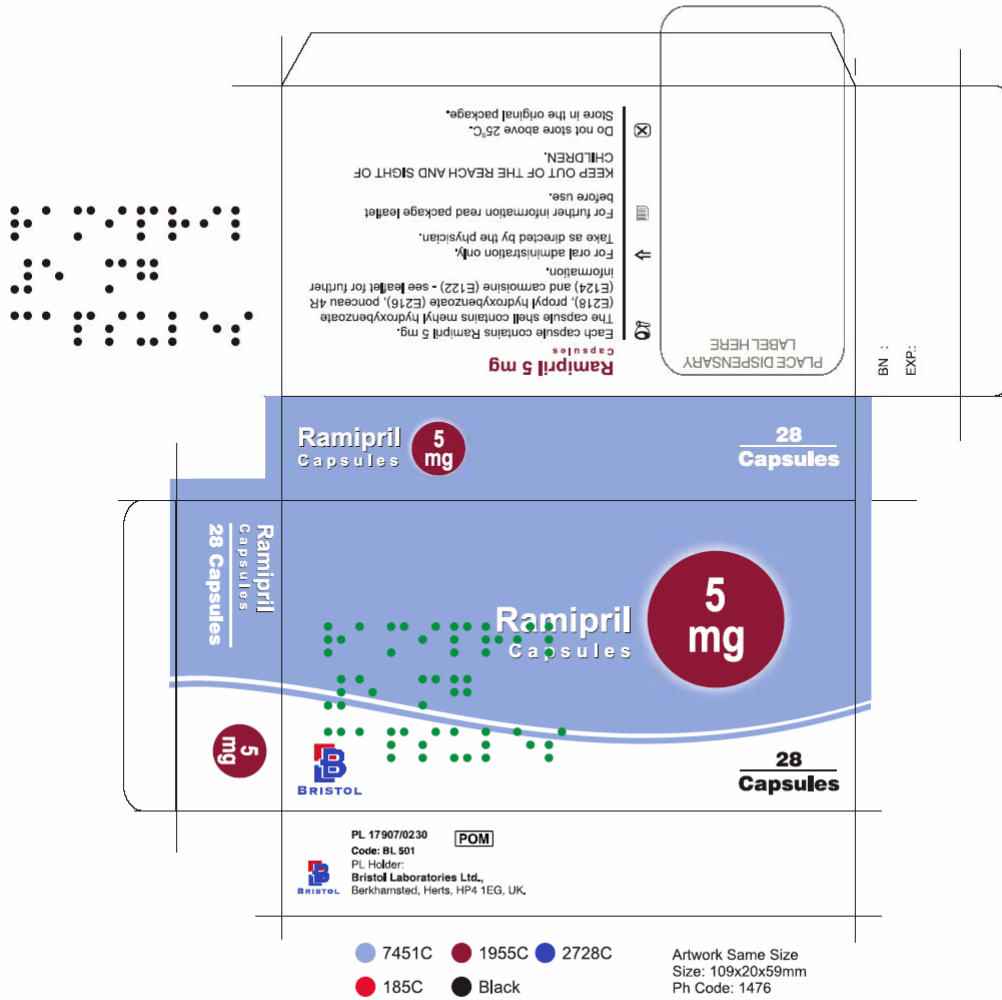
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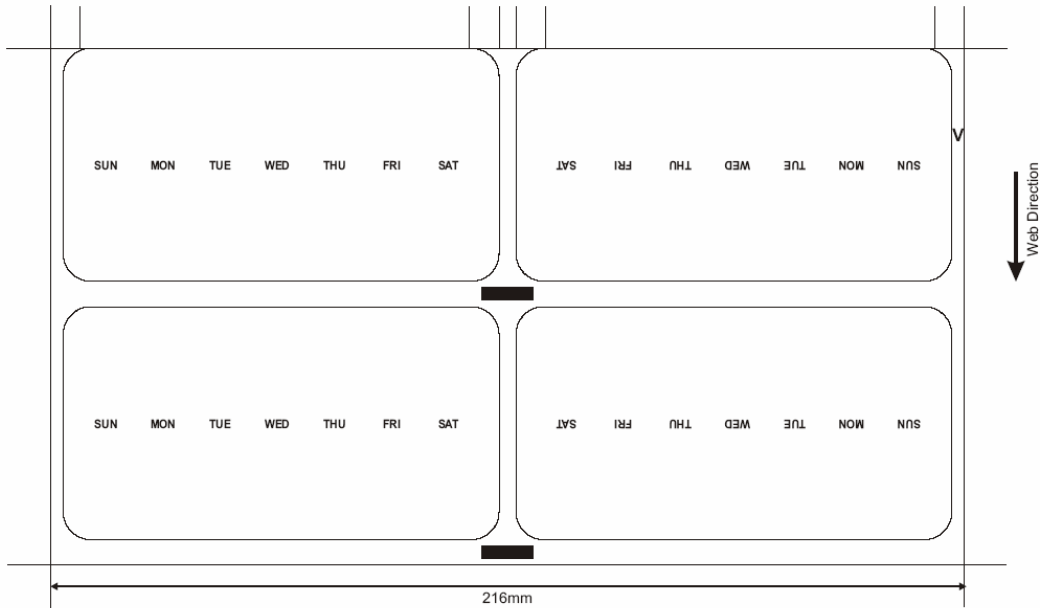
ipca ipca Laboratories Ltd. Regd. Off. - 45, Kandivli Ind. Estate, Mumbai 400 067	
PRODUCT	Ramipril 5 Capsules Carton 28's
DIMENSIONS	109 x 20 x 59 mm
FLAP WIDTH	10 mm
PANTON NOS.	■ Pan 424 C ■ Pan 299 C ■ Pan 207 C
MATERIAL	
ARTIST SIGN DATE	PDC SIGN DATE

Graphic Creations

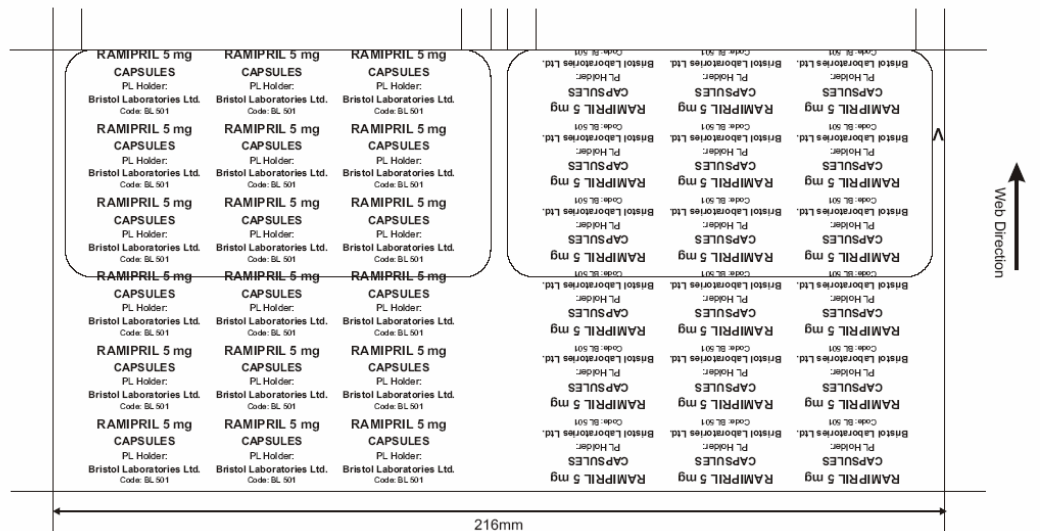
PLEASE NOTE: LASER COPIES ARE SUPPLIED AS A VISUAL REFERENCE ONLY. DO NOT MATCH FOR COLOUR

<p>ARTWORK SPECIFICATION</p> <p>Client: OTC Direct</p> <p>Project: 4477 / A / UK Almus Version 2 Products</p> <p>Item(s): Ramipril 5mg carton artwork</p> <p>Software: Adobe Illustrator 10.0</p>	<p>Fonts: Text outlined</p> <p>Special Colours: ■ PMS 424 ■ PMS 299 ■ PMS 207 ■ CUTTER</p> <p>Please Note: Occasionally conversion of Adobe Illustrator files to final film can result in movement of text. Therefore, artwork and proof(s) must be checked by printer and client against designers proof(s) accompanying this artwork. Colours may also require adjustment for 'trap' and 'overprint' to printer's own specifications.</p>	<p>Checked by: Steve Hobbs</p> <p>Queries regarding this artwork, please contact: Steve Hobbs or Paul Adams</p> <p>Date: 16.1.2006</p> <p>Special Instructions: Cutter shown as Special Colour 'CUTTER', do not print.</p>	<p>32 Dragon Street Peterfield Hampshire GU21 4JJ</p> <p>tel +44 (0)1730 263614 fax +44 (0)1730 263014 e-mail ma@pmdc.co.uk</p> <p style="text-align: center;"></p> <p>The Paul Martin Design Company</p>
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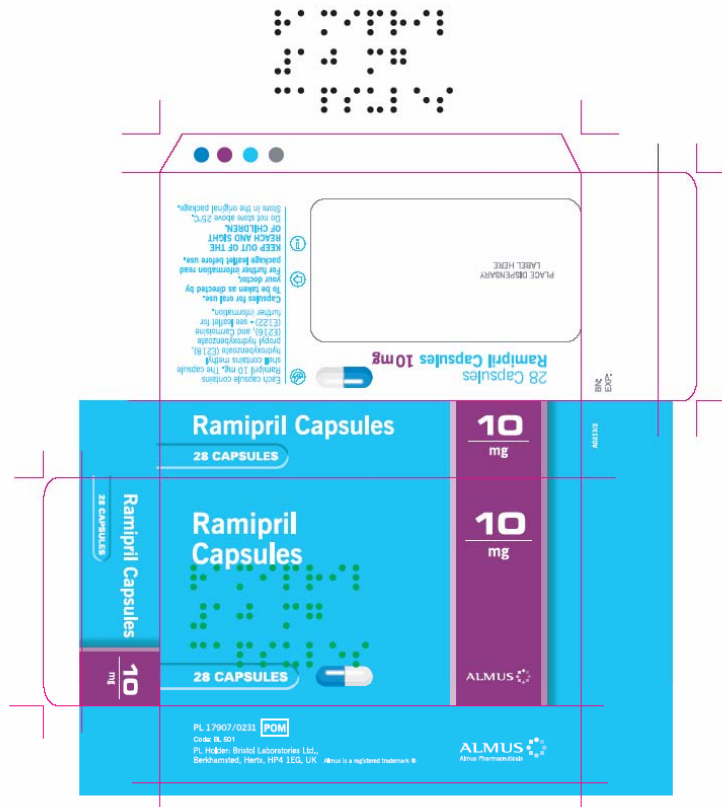




Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61.2 (Length 61.2x10=612.611.5)
 Common Bottom foil for Ramipril 1.25/2.5/5&10
 Graphic Creations



Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61.2 (Length 61.2x10=612.611.5)
 Graphic Creations



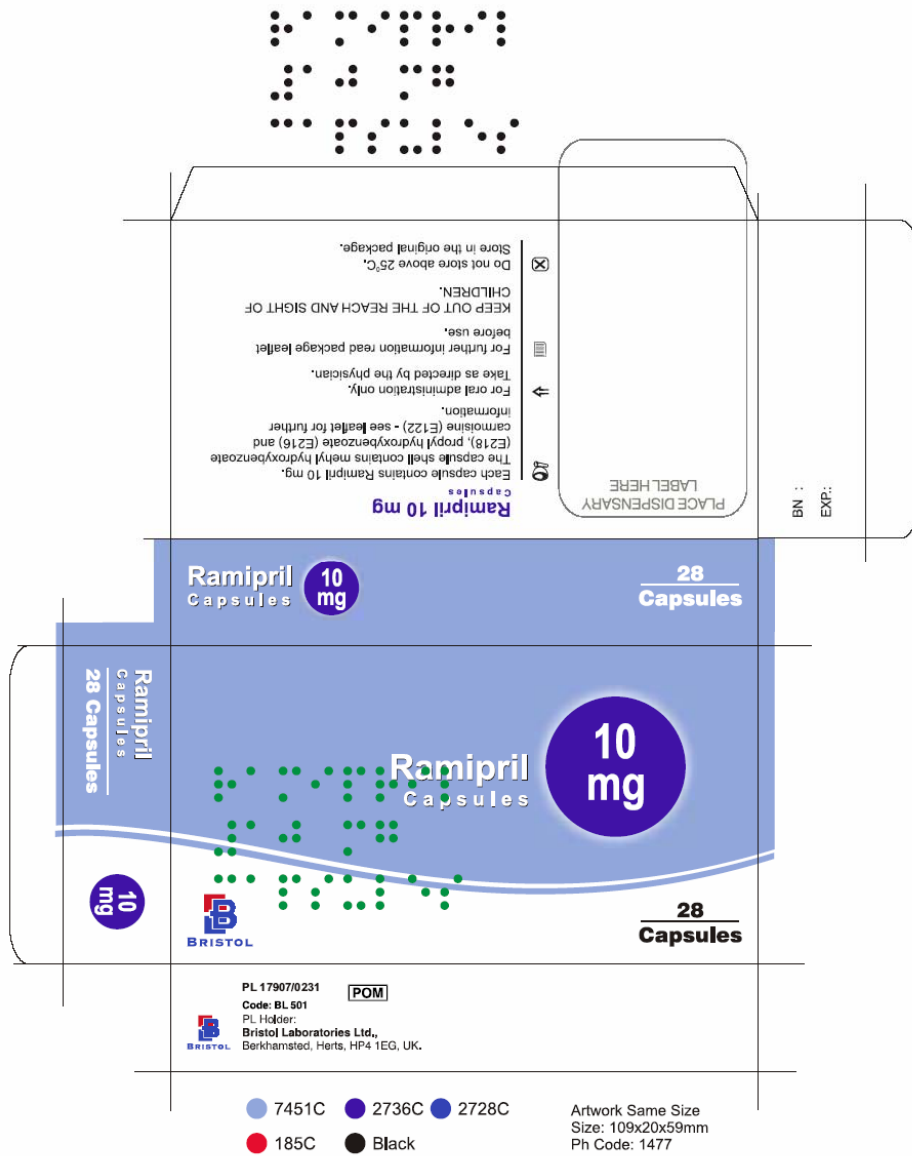
MHRA APPROVED
VERSION: 2
MHRA APPROVAL DATE: TBC
SUPPLIER ISSUE DATE: 23.6.2006

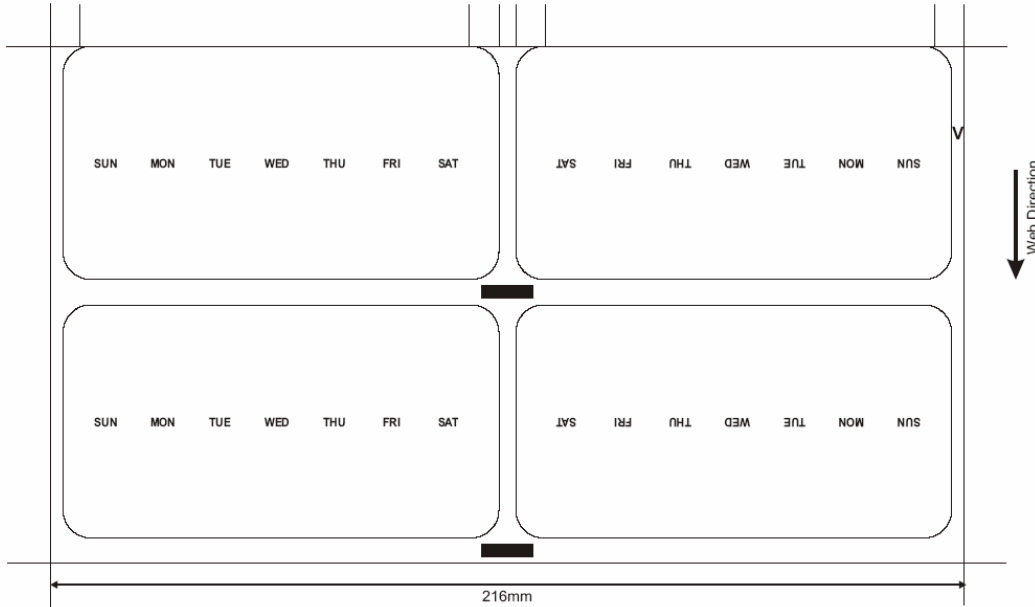
BARCODE 5060057402139
ALMUS CODE A0213/2

ipca ipca Laboratories Ltd. Regd. Off: 45, Kandivli Ind. Estate, Mumbai 400 067	
PRODUCT	Ramipril 10 Capsules Carton 28's
DIMENSIONS	109 x 20 x 59 mm
FLAP WIDTH	10 mm
PANTON NOS.	Pan 424 C Pan 299 C Pan 2613 C Pan 301 C
MATERIAL	
ARTIST SIGN	POC SIGN
DATE	DATE

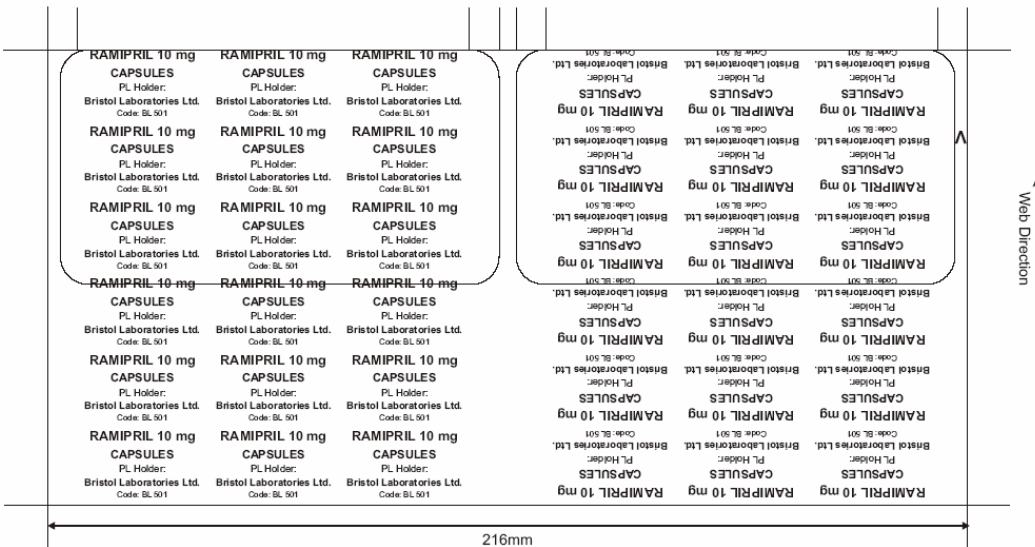
Graphic Creations

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<p>ARTWORK SPECIFICATION</p> <p>Client: OTC Direct</p> <p>Project: 4477 / A / UK Almus Version 2 Products</p> <p>Item(s): Ramipril 5mg carton artwork</p> <p>Software: Adobe Illustrator 10.0</p>	<p>Fonts: Text outlined</p> <p>Please Note: Occasionally conversion of Adobe Illustrator files to final film can result in movement of text. Therefore, filmwork and proof(s) must be checked by printer and client against designers proof(s) accompanying this artwork. Colours may also require adjustment for 'trap' and 'overprint' to printer's own specifications.</p>	<p>Special Colours:</p> <p>PMS 424 PMS 299 PMS 2613 PMS 301</p> <p>CUTTER</p>	<p>Checked by: Steve Hobbs</p> <p>Queries regarding this artwork, please contact: Steve Hobbs or Paul Adams</p> <p>Date: 16.1.2006</p> <p>Special Instructions: Cutter shown as Special Colour 'CUTTER', do not print.</p>
			<p>32 Dragon Street Petersfield Hampshire GU21 4JJ</p> <p>tel: +44 (0)1730 265814 fax: +44 (0)1730 263014 e-mail: mail@pmdc.co.uk</p> <p style="text-align: center;">The Paul Martin Design Company</p>





Black
 Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61,2 (Length 61.2x10=612-611.5)
 Common Bottom foil for Ramipril 1.25/2.5/5&10
 Graphic Creations



Black
 Artwork Same Size
 Size: 216mm
 Layout No.:46 DIO54 13 038
 Pack Size: 55x103mm
 Repeat: 61,2 (Length 61.2x10=612-611.5)
 Graphic Creations