Public Assessment Report

Mutual Recognition Procedure

Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules

Ranace 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules

UK/H/831/01-04

Ranbaxy (UK) Limited
Lay Summary

Ireland, Italy, Poland and Portugal today granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Ramipril/Ranace 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules (Product Licence numbers: 14894/0244-7). These medicines are available by prescription only.

Ranace is the brand name given to this product but, other than differences in the product packaging reflecting this difference in name, Ranace Capsules are identical to Ramipril Capsules. For the remainder of this report, the name Ramipril Capsules will be used to refer to both Ramipril Capsules and Ranace Capsules.

Ramipril Capsules contain the active ingredient ramipril, which belongs to a group of drugs called angiotensin converting enzyme (ACE) inhibitors, which act on the heart and blood vessels. Ramipril Capsules have a number of uses: they can help lower blood pressure if it is too high; they can help the heart pump blood round the body in cases of heart failure; they can prevent the heart getting weaker if you have recently suffered a heart attack; and they can be used to reduce the risk of heart attack, stroke or the need for surgical procedures to increase blood flow to heart.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules outweigh the risks, hence Marketing Authorisations have been granted.
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## Module 1

### Information about initial procedure

| **Name of the product in the Reference Member State** | Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules  
Ranace 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules |
|---------------------------------------------------|--------------------------------------------------|
| **Type of application (Eudratrack details)** | Level 1: Abridged  
Level 2: Initial/Additional strength or form  
Level 3: Generic, Article 10.1  
Level 4: Chemical substance  
Level 5: Prescription only |
| **Name(s) of the active substance(s) (INN)** | Ramipril |
| **Pharmacotherapeutic classification (ATC code)** | ACE Inhibitors, Plain (C09A A05) |
| **Pharmaceutical form and strength(s)** | Hard capsule, 1.25, 2.5, 5 and 10 mg |
| **Reference numbers for the Mutual Recognition Procedure** | UK/H/831/01-04 |
| **Reference Member State** | United Kingdom |
| **Member States concerned** | Ireland, Italy, Poland, Portugal |
| **Date of first authorisation** | 2\textsuperscript{nd} December 2003 |
| **Marketing Authorisation Number(s)** | PL 14894/0244-7 |
| **Date of assessment report** | 10\textsuperscript{th} March 2006 |
| **Name and address of the authorisation holder** | Ranbaxy (UK) Limited, 95 Park Lane, Mayfair, London, W1K 7TE, UK |
Module 2

Summary of Product Characteristics

Summary of Product Characteristics for PL 14894/0244:

1. NAME OF THE MEDICINAL PRODUCT

Ramipril 1.25 mg Capsules
or
Ranace 1.25 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ramipril 1.25 mg.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Hard Capsules. Size 4 with yellow cap/white body imprinted with ‘R’ on cap and ‘1.25’ on body. Contains white to off-white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Ramipril Capsules are indicated for the treatment of mild to moderate hypertension.
Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

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

4.2 Posology and method of administration

Dosage and Administration:

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

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

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

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

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

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

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

*Post myocardial infarction:*

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

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

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

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

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

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

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

### 4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients.

History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients.

Pregnancy. Lactation.

### 4.4 Special warning and precautions for use

**Warnings:**

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

**Precautions:**

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

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

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

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Pregnancy and lactation

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

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

However, ramipril was not fetotoxic in preclinical studies although ACE inhibitors have shown fetotoxicity in some species.

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

In individual cases, as a result of a reduction in blood pressure, treatment with ramipril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

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

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

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

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

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

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

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

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

Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.
**Angioneurotic oedema:** In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with ramipril must be discontinued and appropriate therapy instituted immediately.

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

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

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

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

### 4.9 Overdose

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

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

*ATC-code: C09A A05*

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

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 starch

Capsules Shell

Gelatin
Quinoline yellow (E104)
Ponceau 4R (E124)
Titanium dioxide (E171)

Printing Ink

Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage:

Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container:

Aluminium strips comprising of aluminium foil laminated with LDPE. The strips are enclosed in a cardboard carton in pack sizes of 21, 28, 30, 56 or 60 capsules. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

None

7. MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
Summary of Product Characteristics for PL 14894/0245:

1. NAME OF THE MEDICINAL PRODUCT

Ramipril 2.5 mg Capsules
or
Ranace 2.5 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ramipril 2.5 mg.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Hard Capsules. Size 4 with orange cap/white body imprinted with ‘R’ on cap and ‘2.5’ on body. Contains white to off-white granular powder.

4. CLINICAL PARTICULARS

4.2 Therapeutic indications

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

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

Ramipril Capsules are indicated for the treatment of mild to moderate hypertension.

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

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

Oral administration.

4.2 Posology and method of administration

Dosage and Administration:

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

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

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

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

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.
**Congestive heart failure:** Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25 mg once daily. Depending on the patient's response, the dose may be increased. It is recommended that the dose, if increased, be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10 mg.

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

**Post myocardial infarction:**

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

*Maintenance dose:* 2.5 to 5.0 mg twice a day.

**Dosage adjustment in renal impairment:**

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

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

**Dosage in hepatic impairment:**

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

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

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

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

### 4.3 Contraindications

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

4.4 Special warning and precautions for use

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

Precautions:

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

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

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

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

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

Symptomatic hypotension: In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of ramipril as well as after increasing the dose of ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with ramipril.
If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with ramipril may usually be continued following restoration of effective blood volume and blood pressure.

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

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

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

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

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

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

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered. When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

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

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

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

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

Ramipril should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with ramipril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

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

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

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

Renal: Treatment with ramipril may impair renal function.

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

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.
Allergic: Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of ramipril.

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

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

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

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

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

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: C09A A05

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

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 starch

Capsules Shell

Gelatin
Sunset yellow (E110)
Ponceau 4R (E124)
Titanium dioxide (E171)

Printing Ink

Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage:

Store in the original package. Keep container in the outer carton.
6.5 Nature and contents of container:

Aluminium strips comprising of aluminium foil laminated with LDPE. The strips are enclosed in a cardboard carton in pack sizes of 21, 28, 30, 56 or 60 capsules. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

None

7. MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 14894/0245

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 December 2003

10 DATE OF REVISION OF THE TEXT

28/04/2006

Summary of Product Characteristics for PL 14894/0246:

1. NAME OF THE MEDICINAL PRODUCT

Ramipril 5 mg Capsules
or
Ranace 5 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ramipril 5 mg.

For excipients, see 6.1
3. **PHARMACEUTICAL FORM**

Hard Capsules. Size 4 with maroon cap/white body imprinted with ‘R’ on cap and ‘5’ on body. Contains white to off-white granular powder.

4. **CLINICAL PARTICULARS**

4.3 Therapeutic indications

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

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

Ramipril Capsules are indicated for the treatment of mild to moderate hypertension.

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

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

Oral administration.

4.2 Posology and method of administration

Dosage and Administration:

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

*Hypertension:* The recommended initial dosage in patients not on diuretics and without congestive heart failure is 1.25 mg ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.
A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 - 5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg ramipril, combination treatment is recommended.

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

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

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

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

**Post myocardial infarction:**

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

*Maintenance dose:* 2.5 to 5.0 mg twice a day.

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

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

*Dosage in hepatic impairment:* In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.
Elderly: Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

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

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

4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients.

History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients.

Pregnancy. Lactation.

4.4 Special warning and precautions for use

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

Precautions:

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

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

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

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

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.
Impaired liver function: As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics.
When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered. When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

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

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

4.6 Pregnancy and lactation

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

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

Ramipril should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with ramipril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

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

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

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

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

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

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

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

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

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

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

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

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

4.9 Overdose

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

5.1 Pharmacodynamic properties

ATC-code: C09A A05

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

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 starch

**Capsules Shell**

Gelatin
Carmoisine (E122)
Ponceau 4R (E124)
Brilliant blue (E133)
Titanium dioxide (E171)

**Printing Ink**

Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life
6.4 Special precautions for storage:
Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container:
Aluminium strips comprising of aluminium foil laminated with LDPE. The strips are enclosed in a cardboard carton in pack sizes of 21, 28, 30, 56 or 60 capsules. Not all pack sizes may be marketed.

6.6 Instructions for use and handling
None

7. MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER
PL 14894/0246

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
2 December 2003

10 DATE OF REVISION OF THE TEXT
28/04/2006

Summary of Product Characteristics for PL 14894/0247:

1. NAME OF THE MEDICINAL PRODUCT
   Ramipril 10 mg Capsules
   or
   Ranace 10 mg Capsules
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ramipril 10 mg.

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Hard Capsules. Size 4 with blue cap/white body imprinted with ‘R’ on cap and ‘10’ on body. Contains white to off-white granular powder.

4. CLINICAL PARTICULARS

4.4 Therapeutic indications

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

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

Ramipril Capsules are indicated for the treatment of mild to moderate hypertension.

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

Oral administration.

4.2 Posology and method of administration

Dosage and Administration:

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

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

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

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

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

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

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

**Dosage adjustment in renal impairment:**

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

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

**Dosage in hepatic impairment:**

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

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

**Children:** Ramipril has not been studied in children, and therefore use in this age group is not recommended.
Ramipril Capsules should be taken with a glass of water. The absorption of ramipril is not affected by food.

4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients.

History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients.

Pregnancy. Lactation.

4.4 Special warning and precautions for use

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

Precautions:

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

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

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

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

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

Impaired liver function: As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).
**Symptomatic hypotension:** In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of ramipril and as well as after increasing the dose of ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with ramipril.

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

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

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

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

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

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

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

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.
When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

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

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

4.6 Pregnancy and lactation

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

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

Ramipril should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with ramipril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

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

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

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

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

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

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

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

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

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

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

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

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

Pre-existing proteinuria may deteriorate.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: C09A A05

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 is 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
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 starch

*Capsules Shell*

*Gelatin*

Patent blue (E131)

Titanium dioxide (E171)

*Printing Ink*

Shellac

Propylene glycol

Potassium hydroxide

Black iron oxide (E172)

6.2 Incompatibilities

Not applicable
6.3 Shelf life

2 years

6.4 Special precautions for storage:

Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container:

Aluminium strips comprising of aluminium foil laminated with LDPE. The strips are enclosed in a cardboard carton in pack sizes of 21, 28, 30, 56 or 60 capsules. Not all pack sizes may be marketed.

6.6 Instructions for use and handling

None

7. MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton Street
London
W1K 6TL
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 14894/0247

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 December 2003

10 DATE OF REVISION OF THE TEXT

28/04/2006
Module 3

Product Information Leaflet
Ramipril 1.25 mg Capsules, hard

If you are going to have an operation or need an anaesthetic, tell the doctor or dentist that you are taking Ramipril.

Your doctor may want to do some blood or urine tests while you are taking Ramipril to check that there are no problems with your blood, liver or kidneys.

In case you are taking any of the following agents concomitantly with Ramipril capsules, there are increased chances of changes in your blood picture due to Ramipril.

- Allopurinol (used to treat a condition called gout)
- Immunosuppressants (used to suppress the immune system)
- Corticosteroids (used to treat various conditions including rheumatism, arthritis, allergic conditions, certain skin diseases, asthma or certain blood disorders)

In case you are on dialysis, serious allergic reactions may occur if your machine has component made of high flux polycrylonitrile membranes and dextrane sulphate. This medicine should not be used in such cases.

Taking Ramipril capsules with food and drink

You can take Ramipril with or without meals. Taking it along with alcohol may make you dizzy or sleepy. Consult your doctor.

Pregnancy and breast-feeding

Do not take Ramipril if you are pregnant or planning to become pregnant or if you are breast-feeding.

Driving and using machines

Ramipril can sometimes make people feel faint or dizzy, particularly after starting treatment or after the dose is increased. If you are affected you should not drive or use dangerous machinery. The faint or dizzy feelings may be worse if you drink alcohol at the same time.

Important information about some of the ingredients of Ramipril Capsules

The capsule shell contains small amounts of ponceau 4R (E124). This can sometimes cause allergic reactions.

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 further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets 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 AND WHAT THEY ARE USED FOR

Ramipril belongs to the class of medicines called Angiotensin Converting Enzyme (ACE) inhibitors that act on the heart and blood vessels.

You may have been given Ramipril Capsules to:

- reduce the risk of a heart attack, stroke or the need for heart surgery to improve the blood flow to your heart if you are diabetic patient aged over 55 and have heart problems
- lower your blood pressure if it is too high (a condition called hypertension)
- help your heart pump blood around your body if you have a condition known as congestive heart failure and are also being treated with diuretics (drugs which help to remove excess fluid from the body)

2. BEFORE YOU TAKE RAMIPRIL CAPSULES
**Do not take Ramipril Capsules:**
- If you know you are allergic (hypersensitive) to ramipril or to any of the other ingredients of Ramipril Capsules listed at the end of the leaflet. An allergic reaction may include rash, itching, swelling of face, lips, tongue or hands and feet, or breathing difficulties.
- If you are pregnant or planning to become pregnant or are breast-feeding.
- If you know that you have a condition called angioneurotic oedema where your face, lips, hands or feet swell up, or you have breathing difficulties.
- If you have a condition called renal artery stenosis (narrowing of the artery supplying blood to the kidney).
- If you have low or unstable blood pressure (hypotension).
- If you have faulty heart valves or a condition called outflow obstruction.

Ask your doctor if you are not sure.

**Take special care with Ramipril Capsules:**
- If you have problems with your heart, kidneys and/or liver.
- If you are on haemodialysis (kidney dialysis machine).
- If you have the conditions known as lupus erythematosus or scleroderma.
- If you are taking diuretics (medicines used to increase urine volume) and/or on a low salt diet, or have had diarrhoea and/or vomiting recently.

**Ramipril capsules are not recommended for use in children.**

**Taking other medicine**
Before you start to take Ramipril you must remind your doctor if you are taking any of the following medicines:
- Diuretics, especially the ones that prevent loss of potassium in urine.
- Potassium supplements or potassium containing salt substitutes.
- Other medicines to treat high blood pressure.
- Insulin or other oral medicines to treat diabetes.
- Pain killers called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) used to treat pain and inflammation.
- Lithium used to treat certain mental illnesses.
- Alopurinol (used to treat gout) or corticosteroids or other medicines that depress the immune system.

Make sure you tell your doctor or pharmacist about any other medicines you are taking, or have taken recently, including any bought from a chemist or another shop.

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**3. HOW TO TAKE RAMIPRIL CAPSULES**

Always take Ramipril Capsules exactly as your doctor told you. You should check with your doctor if you are not sure.

Take Ramipril Capsules with a glass of water. They can be taken any time of the day either with or without food. To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.

**Usual doses for adults are:**
To reduce the risk of death due to heart disease, heart attack or stroke, or the need for heart surgery; the usual starting dose is 2.5 mg given once daily. If you have no problems taking Ramipril your doctor may increase your dose to 5 mg once daily after 1 week and to 10 mg once daily after another 3 weeks.

To treat people with raised blood pressure; the usual starting dose is 1.25 mg of Ramipril taken once a day. Your doctor may increase the dose to a maximum of 10 mg daily depending on your response to the treatment. Most people will respond to a daily dose of 2.5 mg to 5 mg. The maximum daily dose should not exceed 10 mg.

If you are taking diuretics already, your doctor may advise you to stop taking diuretics for 2-3 days prior to starting Ramipril. Your doctor may restart treatment with diuretics later if required.

If you have heart failure associated with high blood pressure then your doctor will start treatment with Ramipril in hospital.

To treat congestive heart failure; the usual starting dose is 1.25 mg of Ramipril taken once a day. It is possible that your doctor may have to increase the dose, depending on your response to the treatment. A daily dose of 2.5 mg or more can be taken either as a single dose or in two divided doses. The maximum daily dose should not exceed 10 mg. If you are taking a high dose of diuretics already, your doctor may advise you to reduce the dose of diuretics prior to starting treatment with Ramipril.

If you have had a heart attack, your doctor may start treatment with Ramipril capsules on the 3rd to 10th day after the heart attack, while you are still in the hospital. The treatment will be started with a dose of 2.5 mg twice a day and may be increased or decreased according to your response. Your total daily dose of Ramipril should not exceed 10 mg.

If you are suffering from liver disease, you should not take ramipril in a dose more than 2.5 mg daily.
If you are elderly, you are taking diuretics, or have liver or kidney problems, your doctor may give you a lower dose.

If you have taken more Ramipril Capsules than you should, contact your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some capsules with you so your doctor will know what you have taken.

If you forget to take Ramipril capsules Take your normal dose when it is next due. Do not take a double dose to make up for forgotten doses.

If you stop taking Ramipril capsules Do not stop taking Ramipril even if you feel better. If you stop taking the medicine your symptoms may return. You should check with your doctor or pharmacist if you are not sure.

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

4. POSSIBLE SIDE EFFECTS

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

The assessment of side effects is based on the following frequency categories:

<table>
<thead>
<tr>
<th>Very common:</th>
<th>Common:</th>
</tr>
</thead>
<tbody>
<tr>
<td>more than 1 in 10 patients treated</td>
<td>fewer than 1 in 10, but more than 1 in 100 patients treated</td>
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<table>
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<tr>
<th>Uncommon:</th>
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<tbody>
<tr>
<td>fewer than 1 in 100, but more than 1 in 1,000 patients treated</td>
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<table>
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<tr>
<th>Rare:</th>
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<tbody>
<tr>
<td>fewer than 1 in 1,000, but more than 1 in 10,000 patients treated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Very rare:</th>
</tr>
</thead>
<tbody>
<tr>
<td>fewer than 1 in 10,000 patients treated, including isolated reports</td>
</tr>
</tbody>
</table>

If any of the following happens, stop taking Ramipril capsules and contact your doctor or go to the nearest hospital casualty department immediately:

- Serious rash, hives, itching, chest constriction, shortness of breath or swelling of face, lips, tongue, hands or feet, fainting or a high temperature
- Severe skin reaction with blisters, sores or ulceration.

These are very serious side effects. If you have them you may have had a serious allergic reaction to Ramipril capsules, you may need urgent medical attention or hospitalization.

Tell your doctor if you notice any of the following:

- Redness of skin with itching and hives, rashes, bumps, bruises, or small areas of bleeding under the skin (tiny red dots or larger reddish purple spots)
- You develop rashes or spots on the skin on exposure to light
- Loss of hair and/or nails
- Your fingers or toes become blue when you are cold or emotionally upset (known as Raynaud's Phenomenon)
- Redness and discomfort of the eyes with swelling of the eyelids

The following side effects have been reported commonly:

- Dizziness, headache, fever and tiredness
- Disturbance in sleep, feeling depressed or anxious
- Disturbed balance, nervousness, restlessness, tremors (uncontrolled shaking), confusion
- Decreased appetite
- Tingling or numbness in your hands or toes
- Dry cough, Runny or stuffy nose
- Dry or sore mouth, feeling sick (nausea), being sick (vomiting), abdominal pain, diarrhoea (loose stools) or constipation, indigestion
- Pain in your joints and/or muscles, muscle cramps
- Reduced sexual desire or impotence
- Change or loss of taste.

There may be changes in the results of certain laboratory tests.

- Decrease in the number of blood cells
- Abnormal kidney function tests
- Abnormal liver function tests
- Abnormal level of proteins in urine
- Abnormal levels of sodium or potassium in the blood.

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.

5. HOW TO STORE RAMIPRIL CAPSULES

Keep out of the reach and sight of children

Do not use Ramipril Capsules after the expiry date which is stated on the carton (EXP). The expiry date refers to the last day of that month.
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:
The following side effects have been reported rarely:
- Unusual bleeding or increased tendency to bleed, persistent sore throat and frequent infections (these may occur due to decrease in the number of blood cells).
- Feeling light headed and faint with or without nausea (feeling sick) [especially if you are taking water tablets or suffer from heart failure or are being treated by dialysis].
- Sudden onset of severe abdominal pain with feeling sick or being sick.

The following side effects have been reported commonly:
- Feeling of tightness, heaviness, dull discomfort, or crushing pain that is felt behind the breastbone and may spread to the arms, neck and jaw. It is often brought on by exercise, eating, or stress; or may occur at rest. [These may be manifestations of Angina. Angina occurs due to narrowing of blood vessels, which supply the muscles of the heart, and the resulting failure to deliver enough oxygen for normal functioning of the heart].
- Severe and prolonged chest pain, more than pain in angina as described above, and may be associated with nausea (feeling sick), vomiting (being sick) and excessive sweating. [These may be manifestations of Myocardial Infarction (heart attack)]. Myocardial infarction occurs due to a complete blockade in one or more of the blood vessels, which supply the muscles of the heart, and the resulting failure to deliver oxygen for normal functioning of the heart.
- Sudden onset of a severe headache, dizziness, numbness/weakness in the face, arm, or leg, especially on one side of the body (or) altered speech and mental ability to understand, disturbed vision in one or both eyes, and loss of balance or coordination. [These may be manifestations of stroke].
- Fast or irregular heartbeat.
- Cough with wheezing and tightness in the chest.
- Yellowing of skin and whites of eyes with decreased appetite, abdominal pain (these may be manifestations of a liver problem).
- Swelling of face, ankles or other parts of the body, with sudden increase or decrease in the amount of urine.
- Vasculitis.

Store in the original package.

Medicines should not be disposed off via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ramipril Capsules contains
The active substance is ramipril. Each capsule contains 1.25 mg ramipril.
The other ingredients are Pregelatinised starch (Maize), gelatin, titanium dioxide (E171), quinoline yellow (E104) and ponceau 4R (E124).
The black printing ink contains shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

What Ramipril looks like and contents of the pack
Ramipril 1.25 mg Capsules, hard are yellow and white printed with 'R' on the cap and '1.25' on the body. They contain a white to off-white granular powder.

Ramipril capsules are available as strip packs of 14, 21, 28, 30, 56 and 60 capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder: Ranbaxy (UK) Ltd., 20 Balderton Street, London, W1K 6TL, United Kingdom
Manufacturer: Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co. Tipperary, Republic of Ireland.
Basics GmbH, 201 Hemmelrather Weg, Gebäude G1, Leverkusen 51377, Germany.

This medicinal product is authorised in the Member States of the EEA under the following names:
- Ramipril 1.25 mg Capsules
- Ramipril Ranbaxy 1.25 mg Capsules
- Ramipor
- Ramipril Ranbaxy 1.25 mg Capsules
- Bellramil Capsules 1.25 mg
- Corpril

This leaflet was approved in December 2006.
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 further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets 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

Further information

1. WHAT RAMIPRIL CAPSULES ARE AND WHAT THEY ARE USED FOR

Ramipril belongs to the class of medicines called Angiotensin Converting Enzyme (ACE) inhibitors that act on the heart and blood vessels.

You may have been given Ramipril Capsules to:

- reduce the risk of a heart attack, stroke or the need for heart surgery to improve the blood flow to your heart if you are diabetic patients aged over 55 and have heart problems
- lower your blood pressure if it is too high (a condition called hypertension)
- help your heart pump blood around your body if you have a condition known as congestive heart failure and are also being treated with diuretics (drugs which help to remove excess fluid from the body)

2. BEFORE YOU TAKE RAMIPRIL CAPSULES

If you are going to have an operation or need an anaesthetic, tell the doctor or dentist that you are taking Ramipril.

Your doctor may want to do some blood or urine tests while you are taking Ramipril to check that there are no problems with your blood, liver or kidneys.

In case you are taking any of the following agents concurrently with Ramipril capsules, there are increased chances of changes in your blood picture due to Ramipril.

- Allopurinol (used to treat a condition called gout)
- Immunosuppressants (used to suppress the immune system)
- Corticosteroids (used to treat various conditions including rheumatism, arthritis, allergic conditions, certain skin diseases, asthma or certain blood disorders)

In case you are on dialysis, serious allergic reactions may occur if your machine has component made of high flux polyacrylonitrile membranes and dextrane sulphate. This medicine should not be used in such cases.

Taking Ramipril capsules with food and drink
You can take Ramipril with or without meals. Taking it along with alcohol may make you dizzy or sleepy. Consult your doctor.

Pregnancy and breast-feeding
Do not take Ramipril if you are pregnant or planning to become pregnant or if you are breast-feeding.

Driving and using machines
Ramipril can sometimes make people feel faint or dizzy, particularly after starting treatment or after the dose is increased. If you are affected you should not drive or use dangerous machinery. The faint or dizzy feelings may be worse if you drink alcohol at the same time.

Important information about some of the ingredients of Ramipril Capsules
The capsule shell contains small amounts of sunset yellow (E110) and ponceau 4R (E124). This can sometimes cause allergic reactions.
Do not take Ramipril Capsules:

- If you know you are allergic (hypersensitive) to ramipril or to any of the other ingredients of Ramipril Capsules listed at the end of the leaflet. An allergic reaction may include rash, itching, swelling of face, lips, tongue or hands and feet, or breathing difficulties.
- If you are pregnant or planning to become pregnant or are breast-feeding.
- If you know that you have a condition called angioneurotic oedema where your face, lips, hands or feet swell up, or you have breathing difficulties.
- If you have a condition called renal artery stenosis (narrowing of the artery supplying blood to the kidney).
- If you have low or unstable blood pressure (hypotension).
- If you have faulty heart valves or a condition called outflow obstruction.

Ask your doctor if you are not sure.

Take special care with Ramipril Capsules:

- If you have problems with your heart, kidneys and/or liver.
- If you are on haemodialysis (kidney dialysis machine).
- If you have the conditions known as lupus erythematosus or scleroderma.
- If you are taking diuretics (medicines used to increase urine volume) and/or are on a low salt diet, or have had diarrhoea and/or vomiting recently.

Ramipril capsules are not recommended for use in children.

Take other medicine

Before you start to take Ramipril you must remind the doctor if you are taking any of the following medicines:

- diuretics, especially the ones that prevent loss of potassium in urine.
- potassium supplements or potassium containing salt substitutes.
- other medicines to treat high blood pressure.
- insulin or other oral medicines to treat diabetes.
- pain killers called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) used to treat pain and inflammation.
- lithium used to treat certain mental illnesses.
- allopurinol (used to treat gout) or corticosteroids or other medicines that depress the immune system.

Make sure you tell your doctor or pharmacist about any other medicines you are taking, or have taken recently, including any bought from a chemist or another shop.

3. HOW TO TAKE RAMIPRIL CAPSULES

Always take Ramipril Capsules exactly as your doctor told you. You should check with your doctor if you are not sure.

Take Ramipril Capsules with a glass of water. They can be taken any time of the day either with or without food. To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.

Usual doses for adults are:

To reduce the risk of death due to heart disease, heart attack or stroke, or the need for heart surgery; the usual starting dose is 2.5 mg given once daily. If you have no problems taking Ramipril your doctor may increase your dose to 5 mg once daily after 1 week and to 10 mg once daily after another 3 weeks.

To treat people with raised blood pressure; the usual starting dose is 1.25 mg of Ramipril taken once a day. Your doctor may increase the dose to a maximum of 10 mg daily depending on your response to the treatment. Most people will respond to a daily dose of 2.5 mg to 5 mg. The maximum daily dose should not exceed 10 mg.

If you are taking diuretics already, your doctor may advise you to stop taking diuretics for 2-3 days prior to starting Ramipril. Your doctor may restart treatment with diuretics later if required.

If you have heart failure associated with high blood pressure then your doctor will start treatment with Ramipril in hospital.

To treat congestive heart failure; the usual starting dose is 1.25 mg of Ramipril taken once a day. It is possible that your doctor may have to increase the dose, depending on your response to the treatment. A daily dose of 2.5 mg or more can be taken either as a single dose or in two divided doses. The maximum daily dose should not exceed 10 mg. If you are taking a high dose of diuretics already, your doctor may advise you to reduce the dose of diuretics prior to starting treatment with Ramipril.

If you have had a heart attack, your doctor may start treatment with Ramipril capsules on the 3rd to 10th day after the heart attack, while you are still in the hospital. The treatment will be started with a dose of 2.5 mg two times a day and may be increased or decreased according to your response. Your total daily dose of Ramipril should not exceed 10 mg.

If you are suffering from liver disease, you should not take ramipril in a dose more than 2.5 mg daily.
If you are elderly, you are taking diuretics, or have liver or kidney problems, your doctor may give you a lower dose.

If you have taken more Ramipril Capsules than you should, contact your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some capsules with you so your doctor will know what you have taken.

If you forget to take Ramipril capsules Take your normal dose when it is next due. Do not take a double dose to make up for forgotten doses.

If you stop taking Ramipril capsules Do not stop taking Ramipril even if you feel better. If you stop taking the medicine your symptoms may return. You should check with your doctor or pharmacist if you are not sure.

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

4. POSSIBLE SIDE EFFECTS

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

The assessment of side effects is based on the following frequency categories:

| Very common: | more than 1 in 10 patients treated |
| Uncommon:    | fewer than 1 in 100, but more than 1 in 10 patients treated |
| Rare:        | fewer than 1 in 1,000 patients treated |
| Very rare:   | fewer than 1 in 10,000 patients treated, including isolated reports |

If any of the following happens, stop taking Ramipril capsules and contact your doctor or go to the nearest hospital casualty department immediately:

- Serious rash, hives, itching, chest constriction, shortness of breath or swelling of face, lips, tongue, hands or feet, fainting or high temperature
- Severe skin reaction with blisters, sores or ulceration.

These are very serious side effects. If you have them you may have had a severe allergic reaction to Ramipril capsules. You may need urgent medical attention or hospitalization.

Tell your doctor if you notice any of the following:

- Redness of skin with itching and hives, rashes, bumps, bruises, or small areas of bleeding under the skin (tiny red dots or larger reddish purple spots)
- You develop rashes or spots on the skin on exposure to light
- Loss of hair and/or nails
- Your fingers or toes become blue when you are cold or emotionally upset (known as Raynaud's Phenomenon)
- Redness and discomfort of the eyes with swelling of the eyelids

The following side effects have been reported commonly:

- Dizziness, headache, fever and tiredness
- Disturbance in sleep, feeling depressed or anxious
- Disturbed balance, nervousness, restlessness, tremors (uncontrolled shaking), confusion
- Decreased appetite
- Tingling or numbness in your hands or toes
- Dry cough, runny or stuffy nose
- Dry or sore mouth, feeling sick (nausea), being sick (vomiting), abdominal pain, diarrhoea (loose stools) or constipation, indigestion
- Pain in your joints and/or muscles, muscle cramps
- Reduced sexual desire or impotence
- Change or loss of taste.

There may be changes in the results of certain laboratory tests.

- Decrease in the number of blood cells
- Abnormal kidney function tests
- Abnormal liver function tests
- Abnormal level of proteins in urine
- Abnormal levels of sodium or potassium in the blood.

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.

5. HOW TO STORE RAMIPRIL CAPSULES

Keep out of the reach and sight of children

Do not use Ramipril Capsules after the expiry date which is stated on the carton (EXP). The expiry date refers to the last day of that month.
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

The following side effects have been reported rarely:
- Unusual bleeding or increased tendency to bleed, persistent sore throat and frequent infections (these may occur due to decrease in the number of blood cells)
- Feeling light headed and faint with or without nausea (feeling sick) [especially if you are taking water tablets or suffer from heart failure or are being treated by dialysis]
- Sudden onset of severe abdominal pain with feeling sick or being sick.

The following side effects have been reported commonly:
- Feeling of tightness, heaviness, dull discomfort, or crushing pain that is felt behind the breastbone and may spread to the arms, neck and jaw. It is often brought on by exercise, eating, or stress, or may occur at rest. [These may be manifestations of Angina. Angina occurs due to narrowing of blood vessels, which supply the muscles of the heart, and the resulting failure to deliver enough oxygen for normal functioning of the heart]
- Severe and prolonged chest pain, more than pain in angina as described above, and may be associated with nausea (feeling sick), vomiting (being sick) and excessive sweating. [These may be manifestations of Myocardial Infarction (heart attack). Myocardial Infarction occurs due to a complete blockade in one or more of the blood vessels, which supply the muscles of the heart, and the resulting failure to deliver oxygen for normal functioning of the heart]
- Sudden onset of a severe headache, dizziness, numbness/weakness in the face, arm, or leg, especially on one side of the body (or) altered speech and mental ability to understand, disturbed vision in one or both eyes, and loss of balance or coordination. [These may be manifestations of stroke]
- Fast or irregular heart beat
- Cough with wheezing and tightness in the chest
- Yellowing of skin and whites of eyes with decreased appetite, abdominal pain (these may be manifestations of a liver problem)
- Swelling of face, ankles or other parts of the body, with sudden increase or decrease in the amount of urine
- Vasculitis

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

The active substance is ramipril. Each capsule contains 2.5 mg ramipril.
The other ingredients are pregelatinised starch (Maize), gelatin, titanium dioxide (E171), sunset yellow (E110) and ponceau 4R (E124).
The black printing ink contains shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

What Ramipril looks like and contents of the pack:
Ramipril 2.5 mg Capsules, hard are orange and white and white printed with 'R' on the cap and '2.5' on the body. They contain a white to off-white granular powder.

Ramipril capsules are available as strip packs of 21, 28, 30, 56 and 60 capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder: Ranbaxy (UK) Ltd., 20 Balderton Street, London, W1K 6TL, United Kingdom.

Manufacturer: Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co. Tipperary, Republic of Ireland.
Basics GmbH, 201 Hemmelrather Weg, Gebaude Giz1, Leverkusen 51377, Germany.

This medicinal product is authorised in the Member States of the EEA under the following names:
Ramipril 2.5 mg Capsules
Ramipril Ranbaxy 2.5 mg Capsules
Ramicor
Ramipril Ranbaxy 2.5 mg Cápsulas
Bellramil Capsules 2.5 mg

This leaflet was approved in December 2006.
PATIENT PACKAGE LEAFLET: INFORMATION FOR THE USER:

Ramipril 5 mg Capsules, hard

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 further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets 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
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5. How to store Ramipril Capsules
6. Further information

1. WHAT RAMIPRIL CAPSULES ARE AND WHAT THEY ARE USED FOR

Ramipril belongs to the class of medicines called Angiotensin Converting Enzyme (ACE) inhibitors that act on the heart and blood vessels.

You may have been given Ramipril Capsules to:
- reduce the risk of a heart attack, stroke or the need for heart surgery to improve the blood flow to your heart if you are diabetic patient aged over 55 and have heart problems
- lower your blood pressure if it is too high (a condition called hypertension)
- help your heart pump blood around your body if you have a condition known as congestive heart failure and are also being treated with diuretics (drugs which help to remove excess fluid from the body)

2. BEFORE YOU TAKE RAMIPRIL CAPSULES

anaesthetic, tell the doctor or dentist that you are taking Ramipril. Your doctor may want to do some blood or urine tests while you are taking Ramipril to check that there are no problems with your blood, liver or kidneys.

In case you are taking any of the following agents concomitantly with Ramipril capsules, there are increased chances of changes in your blood picture due to Ramipril.
- Allopurinol (used to treat a condition called gout)
- Immunosuppressants (used to suppress the immune system)
- Corticosteroids (used to treat various conditions including rheumatism, arthritis, allergic conditions, certain skin diseases, asthma or certain blood disorders)

In case you are on dialysis, serious allergic reactions may occur if your machine has component made of high flux polyacrylonitrile membranes and dextrane sulphate. This medicine should not be used in such cases.

Taking Ramipril capsules with food and drink
You can take Ramipril with or without meals. Taking it along with alcohol may make you dizzy or sleepy. Consult your doctor.

Pregnancy and breast-feeding
Do not take Ramipril if you are pregnant or planning to become pregnant or if you are breast-feeding.

Driving and using machines
Ramipril can sometimes make people feel faint or dizzy, particularly after starting treatment or after the dose is increased. If you are affected you should not drive or use dangerous machinery. The faint or dizzy feelings may be worse if you drink alcohol at the same time.

Important information about some of the ingredients of Ramipril Capsules
The capsule shell contains small amounts of the red dyes carmoisine (E122) and ponceau 4R (E124). These can sometimes cause allergic reactions.
Do not take Ramipril Capsules:
- If you know you are allergic (hypersensitive) to ramipril or to any of the other ingredients of Ramipril Capsules listed at the end of the leaflet. An allergic reaction may include rash, itching, swelling of face, lips, tongue or hands and feet, or breathing difficulties.
- If you are pregnant or planning to become pregnant or are breast-feeding.
- If you know that you have a condition called angioneurotic oedema where your face, lips, hands or feet swell up, or you have breathing difficulties.
- If you have a condition called renal artery stenosis (narrowing of the artery supplying blood to the kidney).
- If you have low or unstable blood pressure (hypotension).
- If you have faulty heart valves or a condition called outflow obstruction.

Ask your doctor if you are not sure.

Take special care with Ramipril Capsules:
- If you have problems with your heart, kidneys and/or liver.
- If you are on haemodialysis (kidney dialysis machine).
- If you have the conditions known as lupus erythematosus or scleroderma.
- If you are taking diuretics (medicines used to increase urine volume) and/or are on a low salt diet, or have had diarrhoea and/or vomiting recently.

Ramipril capsules are not recommended for use in children.

Taking other medicine
Before you start to take Ramipril you must remind the doctor if you are taking any of the following medicines:
- Diuretics, especially the ones that prevent loss of potassium in urine.
- Potassium supplements or potassium containing salt substitutes.
- Other medicines to treat high blood pressure.
- Insulin or other oral medicines to treat diabetes.
- Pain killers called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) used to treat pain and inflammation.
- Lithium used to treat certain mental illnesses.
- Allopurinol (used to treat gout) or corticosteroids or other medicines that depress the immune system.

Make sure you tell your doctor or pharmacist about any other medicines you are taking, or have taken recently, including any bought from a chemist or another shop.

If you are going to have an operation or need an anaesthetic, tell your surgeon or dentist that you are taking Ramipril.

3. HOW TO TAKE RAMIPRIL CAPSULES

Always take Ramipril Capsules exactly as your doctor told you. You should check with your doctor if you are not sure.

Take Ramipril Capsules with a glass of water. They can be taken anytime of the day either with or without food. To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.

Usual doses for adults:
To reduce the risk of death due to heart disease, heart attack or stroke, or the need for heart surgery; the usual starting dose is 2.5 mg given once daily. If you have no problems taking Ramipril your doctor may increase your dose to 5 mg once daily after 1 week and to 10 mg once daily after another 3 weeks.

To treat people with raised blood pressure: the usual starting dose is 1.25 mg of Ramipril taken once a day. Your doctor may increase the dose to a maximum of 10 mg daily depending on your response to the treatment. Most people will respond to a daily dose of 2.5 mg to 5 mg. The maximum daily dose should not exceed 10 mg. If you are taking diuretics already, your doctor may advise you to stop taking diuretics for 2-3 days prior to starting Ramipril. Your doctor may restart treatment with diuretics later if required. If you have heart failure associated with high blood pressure then your doctor will start treatment with Ramipril in hospital.

To treat congestive heart failure: the usual starting dose is 1.25 mg of Ramipril taken once a day. It is possible that your doctor may have to increase the dose, depending on your response to the treatment. A daily dose of 2.5 mg or more can be taken either as a single dose or in two divided doses. The maximum daily dose should not exceed 10 mg. If you are taking a high dose of diuretics already, your doctor may advise you to reduce the dose of diuretics prior to starting treatment with Ramipril.

If you have had a heart attack, your doctor may start treatment with Ramipril capsules on the 3rd to 10th day after the heart attack, while you are still in the hospital. The treatment will be started with a dose of 2.5 mg two times a day and may be increased or decreased according to your response. Your total daily dose of Ramipril should not exceed 10 mg.

If you are suffering from liver disease, you should not take ramipril in a dose more than 2.5 mg daily.
If you are elderly, you are taking diuretics, or have liver or kidney problems, your doctor may give you a lower dose.

If you have taken more Ramipril Capsules than you should, contact your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some capsules with you so your doctor will know what you have taken.

If you forget to take Ramipril capsules Take your normal dose when it is next due. Do not take a double dose to make up for forgotten doses.

If you stop taking Ramipril capsules Do not stop taking Ramipril even if you feel better. If you stop taking the medicine your symptoms may return. You should check with your doctor or pharmacist if you are not sure.

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 side effects, although not everybody gets them.'

The assessment of side effects is based on the following frequency categories:

<table>
<thead>
<tr>
<th>Very common:</th>
<th>more than 1 in 10 patients treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>fewer than 1 in 10, but more than 1 in 100 patients treated</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>fewer than 1 in 100, but more than 1 in 1,000 patients treated</td>
</tr>
<tr>
<td>Rare:</td>
<td>fewer than 1 in 1,000, but more than 1 in 10,000 patients treated</td>
</tr>
<tr>
<td>Very rare:</td>
<td>fewer than 1 in 10,000 patients treated, including isolated reports</td>
</tr>
</tbody>
</table>

If any of the following happens, stop taking Ramipril capsules and contact your doctor or go to the nearest hospital casualty department immediately:

- Serious rash, hives, itching, chest constriction, shortness of breath or swelling of face, lips, tongue, hands or feet, fainting or a high temperature
- Severe skin reaction with blisters, sores or ulceration.

These are very serious side effects. If you have them you may have had a serious allergic reaction to Ramipril capsules, you may need urgent medical attention or hospitalization.

rashes, bumps, bruises, or small areas of bleeding under the skin (tiny red dots or larger reddish purple spots)
- You develop rashes or spots on the skin on exposure to light
- Loss of hair and/or nails
- Your fingers or toes become blue when you are cold or emotionally upset (known as Raynaud's Phenomenon)
- Redness and discomfort of the eyes with swelling of the eyelids

The following side effects have been reported commonly:

- Dizziness, headache, fever and tiredness
- Disturbance in sleep, feeling depressed or anxious
- Disturbed balance, nervousness, restlessness, tremors (uncontrolled shaking), confusion
- Decreased appetite
- Tingling or numbness in your hands or toes
- Dry cough, Runny or stuffy nose
- Dry or sore mouth, feeling sick (nausea), being sick (vomiting), abdominal pain, diarrhoea (loose stools) or constipation, indigestion
- Pain in your joints and/or muscles, muscle cramps
- Reduced sexual desire or impotence
- Change or loss of taste.

There may be changes in the results of certain laboratory tests.

- Decrease in the number of blood cells
- Abnormal kidney function tests
- Abnormal liver function tests
- Abnormal level of proteins in urine
- Abnormal levels of sodium or potassium in the blood.

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.

5. HOW TO STORE RAMIPRIL CAPSULES

Keep out of the reach and sight of children

Do not use Ramipril Capsules after the expiry date which is stated on the carton (EXP). The expiry date refers to the last day of that month.
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

The following side effects have been reported:
- Unusual bleeding or increased tendency to bleed, persistent sore throat and frequent infections (these may occur due to decrease in the number of blood cells)
- Feeling light headed and faint with or without nausea (feeling sick) [especially if you are taking water tablets or suffer from heart failure or are being treated by dialysis]
- Sudden onset of severe abdominal pain with feeling sick or being sick.

The following side effects have been reported commonly:
- Feeling of tightness, heaviness, dull discomfort, or crushing pain that is felt behind the breastbone and may spread to the arms, neck and jaw. It is often brought on by exercise, eating, or stress; or may occur at rest. [These may be manifestations of Angina. Angina occurs due to narrowing of blood vessels, which supply the muscles of the heart, and the resulting failure to deliver enough oxygen for normal functioning of the heart]
- Severe and prolonged chest pain, more than pain in angina as described above, and may be associated with nausea (feeling sick), vomiting (being sick) and excessive sweating. [These may be manifestations of Myocardial Infarction (heart attack). Myocardial Infarction occurs due to a complete blockade in one or more of the blood vessels, which supply the muscles of the heart, and the resulting failure to deliver oxygen for normal functioning of the heart]
- Sudden onset of a severe headache, dizziness, numbness/weakness in the face, arm, or leg, especially on one side of the body (or) altered speech and mental ability to understand, disturbed vision in one or both eyes, and loss of balance or coordination. [These may be manifestations of stroke]
- Fast irregular heart beat
- Cough with wheezing and tightness in the chest
- Yellowing of skin and whites of eyes with decreased appetite, abdominal pain (these may be manifestations of a liver problem)
- Swelling of face, ankles or other parts of the body, with sudden increase or decrease in the amount of urine
- Vasculitis

Tell your doctor if you notice any of the following:
- Redness of skin with itching and hives, Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask you pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ramipril contains
The active ingredient ramipril. Each capsule contains 5mg ramipril.
The other ingredients are pregelatinised starch (Maize), gelatin, titanium dioxide (E171), carmoisine (E122), ponceau 4R red (E124) and brilliant blue (E133).

The black printing ink contains shellac, propylene glycol, potassium hydroxide and blackiron oxide (E172).

What Ramipril looks like and contents of the pack
Ramipril 5 mg Capsules, hard are maroon and white printed with 'R' on the cap and '5' on the body. They contain a white to off-white granular powder.

Ramipril capsules are available as strip packs of 14, 21, 28, 30, 56 and 60 capsules. Not all pack sizes may be marketed.

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Basics GmbH, 201 Hemmelrather Weg, Gebäude G1, Leverkusen 51377, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:
- Ramipril 5 mg Capsules
- Ramipril Ranbaxy 5 mg Capsules
- Ramipril
- Ramipril Ranbaxy 5 mg Capsulas
- Bellramil Capsules 5 mg

This leaflet was approved in December 2006
PATIENT PACKAGE LEAFLET: INFORMATION FOR THE USER:

Ramlipril 10 mg Capsules, hard

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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets 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
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6. Further information

1. WHAT RAMIPRIL CAPSULES ARE AND WHAT THEY ARE USED FOR

Ramlipril belongs to the class of medicines called Angiotensin Converting Enzyme (ACE) inhibitors that act on the heart and blood vessels.

You may have been given Ramlipril Capsules to:

- reduce the risk of a heart attack, stroke or the need for heart surgery to improve the blood flow to your heart if you are diabetic patient aged over 55 and have heart problems
- lower your blood pressure if it is too high (a condition called hypertension)
- help your heart pump blood around your body if you have a condition known as congestive heart failure and are also being treated with diuretics (drugs which help to remove excess fluid from the body)

2. BEFORE YOU TAKE RAMIPRIL CAPSULES

Don't take Ramipril Capsules:

- if you know you are allergic

without a prescription

Please notice:

- If you are going to have an operation or need an anaesthetic, tell the doctor or dentist that you are taking Ramipril.
- Your doctor may want to do some blood or urine tests while you are taking Ramipril to check that there are no problems with your blood, liver or kidneys.

Children

Ramipril Capsules are not recommended for use in children.

Taking Ramipril Capsules with food and drink

You can take Ramipril with or without meals. Taking it along with alcohol may make you dizzy or sleepy. Consult your doctor.

Pregnancy and breast-feeding

Do not take Ramipril if you are pregnant or planning to become pregnant or if you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Ramlipril can sometimes make people feel faint or dizzy, particularly after starting treatment or after the dose is increased. If you are affected you should not drive or use dangerous machinery. The faint or dizzy feelings may be worse if you drink alcohol at the same time.

3. HOW TO TAKE RAMIPRIL CAPSULES

Always take Ramlipril exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Dosage

Usual doses for adults are:

- To reduce the risk of death due to heart disease, heart attack or stroke, or the need for heart surgery: The usual starting dose is 2.5 mg given once daily. If you have no problems taking Ramlipril, your doctor may increase your dose to 5 mg once daily after 1 week and to 10 mg once daily after another 3 weeks.
(hypersensitive) to ramipril or to any of the other ingredients of Ramipril Capsules listed at the end of the leaflet. An allergic reaction may include rash, itching, swelling of face, lips, tongue or hands and feet, or breathing difficulties

- If you are pregnant or planning to become pregnant or are breast-feeding
- If you know that you have a condition called angioneurotic oedema where your face, lips, hands, or feet swell up, or you have breathing difficulties
- If you have a condition called renal artery stenosis (narrowing of the artery supplying blood to the kidney)
- If you have low or unstable blood pressure (hypotension)
- If you have faulty heart valves or a condition called outflow obstruction.

Ask your doctor if you are not sure.

Take special care with Ramipril Capsules:
- If you have problems with your heart, kidneys and/or liver
- If you are on haemodialysis (kidney dialysis machine)
- If you have the conditions known as lupus erythematosus or scleroderma
- If you are taking diuretics (medicines used to increase urine volume) and/or are on a low salt diet, or have had diarrhoea and/or vomiting recently.

Taking other medicines
Before you start to take Ramipril you must remind the doctor if you are taking any of the following medicines:
- diuretics, especially the ones that prevent loss of potassium in urine
- potassium supplements or potassium containing salt substitutes
- other medicines to treat high blood pressure
- insulin or other oral medicines to treat diabetes
- painkillers called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) used to treat pain and inflammation
- lithium used to treat certain mental illnesses
- allopurinol (used to treat gout) or corticosteroids or other medicines that depress the immune system.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained

- To treat people with raised blood pressure:
The usual starting dose is 1.25 mg of Ramipril taken once a day. Your doctor may increase the dose to a maximum of 10 mg daily depending on your response to the treatment. Most people will respond to a daily dose of 2.5 mg to 5 mg.
The maximum daily dose should not exceed 10 mg. If you are taking diuretics already, your doctor may advise you to stop taking diuretics for 2-3 days prior to starting Ramipril. Your doctor may restart treatment with diuretics later if required. If you have heart failure associated with high blood pressure then your doctor will start treatment with Ramipril in hospital.

- To treat congestive heart failure:
The usual starting dose is 1.25 mg of Ramipril taken once a day. It is possible that your doctor may have to increase the dose, depending on your response to the treatment. A daily dose of 2.5 mg or more can be taken either as a single dose or in two divided doses.
The maximum daily dose should not exceed 10 mg. If you are taking a high dose of diuretics already, your doctor may advise you to reduce the dose of diuretics prior to starting treatment with Ramipril.

If you are elderly, you are taking diuretics, or have liver or kidney problems, your doctor may give you a lower dose.

Children
Ramipril Capsules should not be given to children.

Methods and routes of administration
Always take Ramipril Capsules exactly as your doctor told you. You should check with your doctor if you are not sure.

Take Ramipril Capsules with a glass of water. Do not chew. They can be taken any time of the day either with or without food. To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.

If you have taken more Ramipril Capsules than you should, contact your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some Capsules with you so your doctor will know what you have taken.
If you forget to take Ramipril Capsules: Take your normal dose when it is next due. Do not take a double dose to make up for forgotten doses.

If you stop taking Ramipril Capsules: Do not stop taking Ramipril even if you feel better. If you stop taking the medicine your symptoms may return. You should check with your doctor or pharmacist if you are not sure.

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

4. POSSIBLE SIDE EFFECTS

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

The assessment of side effects is based on the following frequency categories:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>In fewer than 1 in 10, but more than 1 in 100 patients treated</td>
</tr>
<tr>
<td>Rare:</td>
<td>In fewer than 1 in 1,000, but more than 1 in 10,000 patients treated</td>
</tr>
<tr>
<td>Very serious side effects: If any of the following happens, stop taking Ramipril Capsules and contact your doctor or go to the nearest hospital casualty department immediately:</td>
<td></td>
</tr>
<tr>
<td>Serious rash, hives, itching, chest constriction, shortness of breath or swelling of face, lips, tongue, hands or feet, fainting or a high temperature</td>
<td></td>
</tr>
<tr>
<td>Severe skin reaction with blisters, sores or ulceration.</td>
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</tbody>
</table>

These are very serious side effects. If you have them you may have had a serious allergic reaction to Ramipril Capsules, you may need urgent medical attention or hospitalization.

Serious side effects: Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Cold or emotionally upset (known as Raynaud's phenomenon)
- Redness and discomfort of the eyes with swelling of the eyelids
- Dizziness, headache, fever and tiredness
- Disturbance in sleep, feeling depressed or anxious
- Disturbed balance, nervousness, restlessness, tremors (uncontrolled shaking), confusion
- Decreased appetite
- Tingling or numbness in your hands or toes
- Dry cough, Runny or stuffy nose
- Dry or sore mouth, feeling sick (nausea), being sick (vomiting), abdominal pain, diarrhoea (loose stools) or constipation, indigestion
- Pain in your joints and/or muscles, muscle cramps
- Reduced sexual desire or impotence
- Change or loss of taste.

There may be changes in the results of certain laboratory tests:

- Decrease in the number of blood cells
- Abnormal kidney function tests
- Abnormal liver function tests
- Abnormal level of proteins in urine
- Abnormal levels of sodium or potassium in the blood.

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.

5. HOW TO STORE RAMIPRIL CAPSULES

Keep out of the reach and sight of children.

Do not use Ramipril Capsules after the expiry date which is stated on the carton (EXP). The expiry date refers to the last day of that month.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask you pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Rare:
- Unusual bleeding or increased tendency to bleed, persistent sore throat and frequent infections (these may occur due to decrease in the number of blood cells)
- Feeling lightheaded and faint with cramps or nausea (feeling sick) (especially if you are taking water tablets or suffer from heart failure or are being treated by dialysis)
- Sudden onset of severe abdominal pain with feeling sick or being sick

Common:
- Feeling of tightness, heaviness, dull discomfort, or crushing pain that is felt behind the breastbone and may spread to the arms, neck and jaw. It is often brought on by exercise, eating, or stress; or may occur at rest. (These may be manifestations of angina. Angina occurs due to narrowing of blood vessels, which supply the muscles of the heart, and the resulting failure to deliver enough oxygen for normal functioning of the heart)
- Severe and prolonged chest pain, more than pain in angina as described above, and may be associated with nausea (feeling sick), vomiting (being sick) and excessive sweating. These may be manifestations of myocardial infarction (heart attack). Myocardial infarction occurs due to a complete blockage in one or more of the blood vessels, which supply the muscles of the heart, and the resulting failure to deliver oxygen for normal functioning of the heart.
- Sudden onset of a severe headache, dizziness, numbness/weakness in the face, arm, or leg, especially on one side of the body or altered speech and mental ability to understand, disturbed vision in one or both eyes, and loss of balance or coordination. (These may be manifestations of stroke)
- Fast or irregular heart beat
- Cough with wheezing and tightness in the chest
- Yellowing of skin and whites of eyes with decreased appetite, abdominal pain (these may be manifestations of liver problem)
- Swelling of face, ankles or another parts of the body, with sudden increase or decrease in the amount of urine
- Vasculitis

Other side effects

Tell your doctor if you notice any of the following:

Common:
- Redness of skin with itching and hives, rashes, bumps, bruises, or small areas of bleeding under the skin (tiny red dots or larger reddish-purple spots)
- You develop rashes or spots on the skin on exposure to light
- Loss of hair and/or nails
- Your fingers or toes become blue when you

6. FURTHER INFORMATION

What Ramipril contains

The active ingredient ramipril. Each capsule contains 10mg ramipril

The other ingredients are pregelatinised starch (Maize), gelatin, titanium dioxide (E171) and patent blue (E131).

The black printing ink contains shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

What Ramipril looks like and contents of the pack

Ramipril 10 mg Capsules are blue and white and white printed with 'R' on the cap and '10' on the body. They contain a white to off-white granular powder.

Ramipril Capsules are available as strip packs of 21, 28, 30, 56 and 80 capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder: Ranbaxy (UK) Ltd., 20 Balclerton Street, London W1K 6TL, United Kingdom

Manufacturer: Ranbaxy Ireland Ltd., Spafield, Cork Road, Cashel, Co. Tipperary, Republic of Ireland.
Basics GmbH, 201 Hemmelrather Weg, Gebäude 1, Leverkusen 51377, Germany.

This medicinal product is authorised in the Member States of the EEA under the following names:

Ramipril 10 mg Capsules
Ramipril/Ranbaxy 10 mg Capsules
Ramicor
Ramipril/Ranbaxy 10 mg Capsules
Beliham Capules 10 mg
Corpril

This leaflet was approved on 3rd December 2003

RANBAXY
Module 4

Labelling

1.25 mg strength:
2.5 mg strength:
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<th>RANBAXY</th>
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<tr>
<td><strong>Ramipril</strong>&lt;br&gt;10 mg CAPSULES&lt;br&gt;CODE No.: MP/DRUGS/25/24/83&lt;br&gt;TEAR FOIL IN FROM THE EDGE TO RELEASE CAPSULES</td>
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RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules in the treatment of mild to moderate hypertension, congestive heart failure (as adjunctive therapy to diuretics, with or without cardiac glycosides) and for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures, could be approved. A national marketing authorisation was granted on 2 December 2003.

I EXECUTIVE SUMMARY

I.1 Problem statement

These mutual recognition applications consider generic versions of Ramipril Capsules. The originator product is Tritace 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules (Marketing Authorisation Holder: Aventis Pharma, UK).

The products were granted marketing authorisations in the UK on 2 December 2003. With the UK as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, Ranbaxy UK Limited, is applying for marketing authorisations for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules in Ireland, Italy, Poland and Portugal.

I.2 About the product

Ramipril is a second generation nonsulphhydryl-containing angiotensin converting enzyme (ACE) inhibitor. It is a prodrug and is hydrolysed in vitro to release the active metabolite ramiprilat, which has a long elimination half life, permitting once daily administration. Ramiprilat is a reversible, slow- and tight-binding inhibitor of ACE. It decreases plasma levels of angiotensin (ANG) II and aldosterone, and potentiates the effects of bradykinin. Most of the beneficial hemodynamic effects of ramiprilat result from decreased angiotensin II formation, which, in turn, decreases vasopressor activity and peripheral resistance. There is evidence to suggest that the local inhibition of ACE and angiotensin II formation in specific target tissues such as the vascular wall may be involved in the haemodynamic effects of ramipril. ACE inhibition potentiates endogenous bradykinin levels, which may contribute to at least two potentially beneficial cardiac effects, i.e. regression of left ventricular hypertrophy and a cardioprotective effect on the ischaemic myocardium.

When administered to patients with essential hypertension ramipril decreases both systolic and diastolic blood pressure in a dose dependent manner, without affecting heart rate or the normal circadian variation of blood pressure. The antihypertensive response is maintained even after 24 hours of ramipril administration. Treatment with ramipril causes regression of pathological left ventricular hypertrophy and may thus prevent the serious long term complications of hypertension.

Ramipril has shown variable effects on renal blood flow in patients with normal renal function. Like other ACE inhibitors, ramipril reduces the urinary excretion of proteins in both normotensive and hypertensive patients with proteinuric renal disease.
I.3 The development programme
The objective of the development programme was to formulate a robust, stable, acceptable formulation of Ramipril Capsules comparable in performance to Tritace Capsules (Aventis Pharma, UK), which are the reference products for these generic applications.

I.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles
No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Drug substance
An EDQM certificate of suitability has been provided for the production of ramipril at the two manufacturing facilities used in the manufacture of active substance for this product.

The active substance specification is in accordance with the current pharmacopoeial monograph, with some additional limits imposed. A retest interval of 24 months has been agreed.

Drug product
The finished product is manufactured and assembled at a suitable site. This facility is responsible for all steps in the manufacture of the finished product, assembly/packaging, quality control, stability testing and export to the EEA. Batch release in the EEA is performed by Ranbaxy Ireland Limited, Co Tipperary, Ireland, and Basics GmbH, Leverkusen, Germany.

The objective of the development programme was to formulate a robust, stable, acceptable formulation of Ramipril Capsules comparable in performance to Tritace Capsules (Aventis Pharma, UK), which are the reference products for these generic applications. The finished product is packaged in aluminium strips, composed of aluminium laminated with LDPE. Each pack contains 21, 28, 30, 56 or 60 tablets. The packaging materials comply with the European Pharmacopoeia. The active substance does not contain materials of animal origin. The applicant has provided certificates of suitability for TSE for all manufacturers of gelatin used to produce the capsules. No other excipients contain materials of animal origin.
A bioequivalence study measuring pharmacokinetic parameters $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\text{inf}}$ of patients treated with the Ranbaxy product versus Tritace capsules showed bioequivalence between the two products.

The proposed finished product specifications are in compliance with the general pharmacopoeial requirements and regulatory standards. The product shelf life of 24 months, with the storage directions “Store in original package. Keep the container in the outer carton”, have been justified by stability data provided.

II.2 Non-clinical aspects

The assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The applicant's expert provides a sufficiently comprehensive overview of the pharmacology and toxicology of ramipril. No new preclinical toxicology data were submitted, which is acceptable given the nature of the application.

II.3 Clinical aspects

The application contains an adequate review of published clinical data. No new toxicology, pharmacokinetic or pharmacodynamic data were submitted for this application and none were required. Data from a single bioequivalence study, comparing the plasma kinetics of Ramipril 10 mg Capsules from Ranbaxy with Tritace 10 mg Capsules (Aventis Pharma, UK), showed bioequivalence between the two tablets (according to the CPMP criteria).

Regarding safety, no serious or unexpected adverse events were observed in the bioequivalence study and the expert report identifies no new safety issues.
REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION
None Required. The product manufacturer has been inspected by the relevant authorities and satisfactory GMP certification has been provided.

Batch release into the EEA is conducted by Ranbaxy Ireland Limited or Basics GmbH, (Germany). Copies of manufacturing authorisations have been provided from the respective national authorities.

INTRODUCTION
These abridged applications are for immediate-release capsules containing 1.25 mg, 2.5 mg, 5 mg and 10 mg ramipril, which are essentially similar and cross refer to Tritace 1.25 mg, 2.5 mg, 5 mg and 10 mg capsules (PL 13402/0021-4); the UK brand leaders marketed by Hoescht Marion Roussel Limited (trading as Aventis Pharma). Tritace 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules were first authorised in the UK on 28 November 1989. Thus, the 10-year period of exclusivity rule is satisfied.

The capsules are intended for reducing the risk myocardial infarction (MI), stroke, cardiovascular death or the need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina, multivessel CABG (coronary artery bypass graft) or multivessel PTCA (percutaneous transluminal coronary angioplasty)), stroke or peripheral vascular disease. They are also indicated for reducing the risk of MI, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings: hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 90 mmHg); high total cholesterol (> 5.2 mmol/L); low HDL (< 0.9 mmol/L); current smoker; known microalbuminuria; or clinical evidence of previous vascular disease. Additionally, the capsules are indicated for the treatment of mild to moderate hypertension and congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

ACTIVE SUBSTANCE

GENERAL INFORMATION

Nomenclature
Ramipril, which is described in the European Pharmacopoeia, has the chemical name: (2S,3aS,6aS)-1-[(S)-2-[(S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]octahydro-cyclopenta[b]pyrrole-2-carboxylic acid. CAS number: 87333-19-5.

General Properties
A white or almost white crystalline powder. It is slightly soluble in water and freely soluble in methanol. A 0.3 % solution exhibits a pH of 4.44. The molecule is dextro-rotatory, with five chiral centres and specific optical rotation of +32.0 to +38.0° on dried basis.
MANUFACTURE

Manufacturer
A certificate of suitability has been granted to ramipril made by the active substance manufacturer.

Description of Process and Controls
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.

Control of Materials
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.

Control Critical Steps and Intermediates
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.

Process Validation
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.

Manufacturing Process Development
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.

CHARACTERISATION

Elucidation of Structure and Other Characteristics
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.

Impurities
Related substances are controlled in accordance with the pharmacopoeial monograph and a suitable limit for other unidentified impurities is included in the specification. Residual solvents are approximately controlled in the specification. The EDQM CEP supports the suitability of the monograph, with additional specified controls for impurities, from this manufacturer.

CONTROL OF ACTIVE SUBSTANCE

The active substance specification is provided and is satisfactory.

Specifications applied on the active substance at the Finished Product Manufacturing Site are the same as those of the active substance manufacturer, with an additional control of physical parameters.

Satisfactory batch data from both manufacturing sites has been provided;

Reference Standards or Materials
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.
Container Closure System
An EDQM CEP has been provided in support of the suitability of active substance from the proposed source. This is acceptable.

Stability
A retest interval of 24 months is stated in the CEP; this is therefore acceptable.

MEDICINAL PRODUCT

DESCRIPTION AND COMPOSITION OF THE MEDICINAL PRODUCT
The qualitative composition of Ramipril Capsules is as follows:

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>Active</td>
</tr>
<tr>
<td>Pregelatinised starch</td>
<td>Binder, disintegrant &amp; diluent</td>
</tr>
<tr>
<td><strong>Total fill weight</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CAPSULE</strong></td>
<td></td>
</tr>
<tr>
<td>Quinoline Yellow</td>
<td>Shell cap pigment</td>
</tr>
<tr>
<td>Sunset Yellow</td>
<td>Shell cap pigment</td>
</tr>
<tr>
<td>Carmoisine</td>
<td>Shell cap pigment</td>
</tr>
<tr>
<td>Brilliant blue</td>
<td>Shell cap pigment</td>
</tr>
<tr>
<td>Patent blue</td>
<td>Shell cap pigment</td>
</tr>
<tr>
<td>Ponceau 4R</td>
<td>Shell cap pigment</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>Shell cap opacifier</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Shell cap</td>
</tr>
<tr>
<td>Purified water</td>
<td>Shell cap solvent <em>qs</em></td>
</tr>
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<td>Titanium dioxide</td>
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<tr>
<td><strong>PRINTING INK</strong></td>
<td></td>
</tr>
<tr>
<td>Shellac</td>
<td>Printing ink</td>
</tr>
<tr>
<td>Dehydrated alcohol</td>
<td>Printing ink</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>Printing ink</td>
</tr>
<tr>
<td>Butyl alcohol</td>
<td>Printing ink</td>
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<tr>
<td>Propylene glycol</td>
<td>Printing ink</td>
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<tr>
<td>Strong ammonia soln.</td>
<td>Printing ink</td>
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<tr>
<td>Black iron oxide</td>
<td>Printing ink</td>
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<tr>
<td>Potassium hydroxide</td>
<td>Printing ink</td>
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<tr>
<td>Purified water</td>
<td>Printing ink</td>
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A stability overage is included for each strength. This is acceptable on the basis of the stability data provided.
PHARMACEUTICAL DEVELOPMENT

Composition Optimisation
Compatibility studies have been described during the selection of excipients, leading to the choice of pregelatinised starch as the sole excipient. This single component was found to have satisfactory compressibility, binding properties and lubricity.

The composition was chosen in order to achieve satisfactory processing properties and also a scalable formulation for use in all of the strengths. The 1.25, 2.5 and 5 mg all use a common blend, while the 10 mg strength is slightly adjusted.

Essential Similarity
The product contains the same quantitative composition of active ingredient and is the same pharmaceutical form (oral immediate release) as the corresponding strength of the UK originator product. The qualitative composition of the active substance and establishment of bioequivalence is discussed in this assessment report.

Clinical Trial Formulation
The 10 mg formulation was used for bioequivalence testing. This was of the same composition as that proposed for marketing.

Manufacturing Process Optimisation
Satisfactory development studies were carried out in order to optimise the manufacturing process.

MANUFACTURE
Process
Satisfactory details of the manufacturing process for Ramipril Tablets are provided.

Validation
Satisfactory information has been provided in relation to validation of the manufacturing process.

Control of Excipients
The excipients present in the product are stated under composition. Ranbaxy perform internal testing on the hard gelatin capsules according to a suitable specification. Satisfactory certificates of analysis have been provided for pregelatinised starch and gelatin capsules.

Control of Medicinal Product
Ramipril capsules are tested to an appropriate in-house specification on release. The shelf life specification incorporates the same tests as release, with some widened limits.

Analytical Validation
The validation reports were satisfactory.

Batch Data
The batch data demonstrate consistent compliance with the finished product specification.

Reference Standards or Materials
Reference standards for ramipril and related substances have been stated and a certificate of analysis has been provided for ramipril reference standard used during method validation.
Container Closure System
Ramipril capsules are packaged in:

1) Aluminium / LDPE strips in cardboard outer for marketing. Pack sizes 21, 28, 30, 56 and 60.

Satisfactory specifications have been described for the Al / LDPE strip.

Stability

Al/LDPE strip stability
Representative batches have been tested under appropriate storage conditions in accordance with relevant regulatory guidance.

All stability results for product stored in the aluminium strips were satisfactory.

A commitment has been given to perform full stability testing on commercial scale batches of each strength.

The approved shelf life is 24 months, when stored according to the conditions “Store in the original package. Keep the container in the outer carton”. The statement on conditions is satisfactory.

REGIONAL INFORMATION
Process validation protocol included.

SUMMARY OF PRODUCT CHARACTERISTICS
Pharmaceutically satisfactory

BIOEQUIVALENCE
The data submitted by the MA holder indicate that satisfactory bioequivalence has been demonstrated. For further discussion, see the medical assessment report.

Satisfactory validation of the method for the quantitation of ramipril and ramiprilat has been presented.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY
The applicant’s products have the same quantitative and qualitative composition in terms of active substances, the same pharmaceutical form and are bioequivalent to the originator product. Conditions for essential similarity have been met.

Acceptable quality standards have been defined and evidence of reproducible manufacture and assurance of compliance with the specification over the shelf life has been provided.
These applications for a generic product claim essential similarity to Tritace Capsules (Aventis Pharma) which has been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications, however, a preclinical expert report, summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.
1. INTRODUCTION
This is a mainstream, national, abridged, complex licensing application for Ramipril Capsules, submitted under article 10.1 of the EEC Directive 2001/83. The applicant is claiming essential similarity to Tritace Capsules (PL 13402/0021-4) for which a UK licence was granted to Aventis Pharma Ltd in November 1989.

2. BACKGROUND
Ramipril is a once daily angiotensin-converting enzyme inhibitor. It inhibits the conversion of angiotensin I to angiotensin II.

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

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

Ramipril Capsules are indicated for the treatment of mild to moderate hypertension. Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

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

Oral administration.

Assessor's Comment
These indications are consistent with those of the cross-referenced product licence and are satisfactory.

4. DOSE & DOSE SCHEDULE
These are in line with those of the cross-referenced product licence.
5. **TOXICOLOGY**
No new data are submitted or required.

6. **CLINICAL PHARMACOLOGY**
   
6.1 **Pharmacodynamics**
Ramipril inhibits the angiotensin converting enzyme (ACE). The angiotensin converting enzyme is a peptidyl-dipeptidase, catalysing the conversion of angiotensin I to the vasocontracting peptide, angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II concentration, resulting in increased plasma renin activity (because of removal of the negative feedback from the renin release) and a reduction in aldosterone secretion.

ACE is identical to kininase-II. Therefore Ramipril may also block the decomposition of bradykinin, which is a potential vasodepressive peptide. To which extent this has an importance for the therapeutic effect of Ramipril has not yet been elucidated.

Although the mechanism by which Ramipril decreases blood pressure is anticipated to be primarily a suppression of the renin-angiotensin-aldosterone system, it is shown that Ramipril also has an antihypertensive effect in patients with low-renin hypertension.

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

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13–17 hours for 5–10 mg ramipril, and markedly longer for the lower doses of 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.

6.3 **Bioequivalence**
The applicant has submitted a single dose bioequivalence study. This was an open randomised, two treatment, two sequence, two period, single dose, cross-over comparative bio-availability study of Ramipril 10 mg capsules (Product T) of Ranbaxy Laboratories Ltd and Tritace 10 mg capsules (Product R) of Aventis Pharma in 32 healthy, adult male human subjects, under fasting conditions. Both periods were separated by a washout of 14 days.

The pharmacokinetic findings reported are satisfactory and demonstrate that the test product, Ramipril 10 mg tablets of Ranbaxy Laboratories Ltd is bio-equivalent to the reference product, Tritace® 10 mg tablets of Aventis Pharma Ltd.
The essentially linear pharmacokinetics of Ramipril makes it likely that the lower-dose Ramipril formulations also are bioequivalent to the corresponding marketed brand formulations, although bioequivalence has not been assessed explicitly.

Five adverse events in five subjects were reported and these were: giddiness (three), cough (one) and loose stools (one). No serious adverse events were reported.

Assessor’s Comment
The study design, analytical methodology and statistical evaluation of the presented bioequivalence trials are in accordance with the recommendations of the relevant CPMP guidelines: ‘Investigation of bioavailability and bioequivalence.’ Therefore, the bioequivalence of the generic products with the referenced innovator products, marketed in UK by Aventis Pharma Ltd, has been proven.

7. EFFICACY
No new efficacy data are presented for this application and none are required. However, the applicant has provided a critical and extensive review of clinical trials published in the literature regarding the efficacy and safety of Ramipril in patients with hypertension and heart failure.

8. SAFETY
No new safety data are provided or needed. But the applicant has provided a brief safety review of Ramipril. No new safety issues have been identified. The clinical safety of Ramipril is well established following over 15 years of experience regarding its clinical use. The most commonly reported adverse events were mild in nature (mainly symptoms associated with hypertension at the beginning of therapy or cough) and transient. However, a small proportion of treated patients subsequently discontinue therapy due to side effects.

Both in hypertensives and heart failure patients with symptomatic hypotension, functional renal insufficiency and hyperkalaemia are predictable consequences of interference with the renin-angiotensin system. Deterioration of renal function during treatment has mainly been reported in patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis.

Rarely reported serious adverse events associated with Ramipril treatment include angioedema, bone marrow depression, fulminant hepatic necrosis and life threatening anaphylactoid reactions, including severe skin reactions like toxic epidermal necrolysis, steven-johnson-syndrome, pemphigus and erythema multiforme.

9. EXPERT REPORT
A satisfactory Clinical Expert Report has been submitted with an appropriate CV.

10. SUMMARY OF PRODUCT CHARACTERISTICS
The text of the proposed SPC is essentially the same as that of the cross-reference product licence and is therefore satisfactory.
11. DISCUSSION
ACE-inhibitors such as Ramipril have been available in the UK for over 10 years. The use of Ramipril is well established. It has recognised efficacy and acceptable safety.

With regards to the current application, sufficient clinical information has been submitted. When used as indicated Ramipril has a favourable benefit-to-risk ratio. The hazard associated with Ramipril appears to be low and acceptable when considered in relation to its therapeutic benefits.

12. CONCLUSION
Marketing authorisation may be granted, subject to the resolution of the outstanding point outlined in the recommendations below.

13. RECOMMENDATIONS
A Marketing authorisation may be granted.
5. Overall conclusion

QUALITY

The important quality characteristics of Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

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

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. 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.
Module 6

Steps take after initial procedure

No further steps have yet been taken following initial procedure.