Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ramic 10 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 10 mg of ramipril.

Excipient with known effect:
Ponceau 4R: 0.12mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule
Purple opaque body and purple opaque cap. Dimensions 14.3 x 5 mm. The body has "RP 10" printed in black containing a white or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of hypertension.

Cardiovascular prevention: reduction of cardiovascular morbidity and mortality in patients with:

- manifest atherothrombotic cardiovascular disease (history of coronary heart disease or stroke, or peripheral vascular disease) or
- diabetes with at least one cardiovascular risk factor (see section 5.1).

Treatment of renal disease:

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

Treatment of symptomatic heart failure.

Secondary prevention after acute myocardial infarction: reduction of mortality from the acute phase of myocardial infarction in patients with clinical signs of heart failure when started > 48 hours following acute myocardial infarction.

4.2 Posology and method of administration

Oral administration. It is recommended that Ramic is taken each day at the same time of the day. Ramic capsules should be taken with plenty of liquid. It must not be chewed or crushed. Ramic can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2).

Adults

Hypertension:
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control.
Ramic may be used in monotherapy or in combination with other classes of antihypertensive medicinal products (see sections 4.3, 4.4, 4.5 and 5.1).

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

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

Diuretic treated patients:
Hypotension may occur following initiation of therapy with Ramic; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2-3 days before beginning therapy with Ramic to reduce the likelihood of symptomatic hypotension. If the diuretic cannot be discontinued, the initial dose of Ramic should be 1.25mg. In hypertensive patients in whom the diuretic is not discontinued, therapy with Ramic should be initiated with a 1.25 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Ramic should be adjusted according to blood pressure target.

Cardiovascular prevention:

Starting dose
The recommended initial dose is 2.5 mg of Ramic once daily.

Titration and maintenance dose
Depending on the patient's tolerability to the active substance, the dose should be gradually increased. It is recommended to double the dose after one or two weeks of treatment and - after another two to three weeks - to increase it up to the target maintenance dose of 10 mg Ramic once daily.
See also posology on diuretic treated patients above.

Treatment of renal disease:
In patients with diabetes and microalbuminuria

Starting dose
The recommended initial dose is 1.25 mg of Ramic once daily.

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

In patients with diabetes and at least one cardiovascular risk

Starting dose
The recommended initial dose is 2.5 mg of Ramic once daily.

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

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

Starting dose
The recommended initial dose is 1.25 mg of Ramic once daily.

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

Symptomatic heart failure:

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

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

Secondary prevention after acute myocardial infarction and with heart failure:

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

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

Special populations

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

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 reduced to a diminished activity of esterases in the liver, resulting in elevated plasma Ramipril levels. Treatment with Ramic should therefore be initiated with a reduced dose under close medical supervision in patients with impaired hepatic function. The maximum daily dose is 2.5 mg Ramic in patients with hepatic impairment.

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

Paediatric Population
The safety and efficacy of ramipril in children has not yet been established.

Currently available data for ramipril are described in sections 4.8, 5.1, 5.2 & 5.3 but no specific recommendation on posology can be made.

4.3 Contraindications

Hypersensitivity to Ramipril, any other ACE (Angiotensin Converting Enzyme) inhibitors, or any of the excipients (see section 6.1).

History of angioneurotic oedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs).

Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)

Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.

Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney.
Second and third trimesters of pregnancy (see section 4.4 and 4.6).

Use in children.

The concomitant use of Ramic with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Special populations

Pregnancy

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

Patients at particular risk of hypotension:

- *Patients with strongly activated renin-angiotensin-aldosterone system*

Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.
Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:
- patients with severe hypertension
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)
- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension.

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

- *Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the

combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

- *Transient or persistent heart failure post MI*

- *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*
The initial phase of treatment requires special medical supervision.

Elderly patients

See section 4.2.

Surgery

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

Monitoring of renal function

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

Impaired renal function

Patients with renal insufficiency may require reduced or less frequent doses of Ramic; their renal function should be closely monitored. In the majority, renal function will not alter. Particularly careful monitoring is required in patients with renal impairment (see section 4.2). There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation. This may be related to the functional role of angiotensin II in maintaining glomerular filtration pressure. It may not be possible to achieve a maximal response in blood pressure and maintain adequate renal perfusion. 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 haemodialysis.

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 Ramic is given, in particular concomitantly with a diuretic. Dosage reduction of Ramic 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 Ramic as well as after increasing the dose of Ramic. It is more likely occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or in 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 Ramic.

Agranulocytosis and bone marrow depression

In patients on angiotensin converting enzyme inhibitors, agranulocytosis and bone marrow depression have been seen rarely, as may a reduction in red cell count, haemoglobin content and platelet count. This is more frequent in patients with renal impairment, especially if they also have collagen vascular disease. No cases of agranulocytosis and neutropenia have been reported to date with Ramic. However, 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 antimetabolites.

Angioedema

Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). This risk may be increased in patients taking concomitant medications such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus); vildagliptin or racecadotril.
In case of angioedema, Ramic must be discontinued.
Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms. Intestinal angioedema has been reported in patients treated with ACE inhibitors including Ramic (see section 4.8).
These patients presented with abdominal pain (with or without nausea or vomiting).

Anaphylactic reactions during desensitization

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

Electrolye monitoring: Hyperkalaemia

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

Electrolyte Monitoring: Hyponatraemia

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Neutropenia/agranulocytosis

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

Ethnic differences

ACE inhibitors cause higher rate of angioedema in black patients than in non-black patients.

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

Cough

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

Ramipril 10mg capsules contain the colourant Ponceau 4R (E124) which cause allergic reactions.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interactions

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Contra-indicated combinations

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

Precautions for use

Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim and in fixed dose combination with sulfamethoxazole, tacrolimus, ciclosporin): Hyperkalaemia may occur; therefore close monitoring of serum potassium is required.

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

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

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

Lithium salts: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium level must be monitored.
Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Blood glucose monitoring is recommended.

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

mTOR inhibitors or DPP-IV inhibitors: An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin. Caution should be used when starting therapy (see section 4.4).

Racecadotril: A potential increased risk of angioedema has been reported for a concomitant use of ACE inhibitors and NEP inhibitor such as racecadotril (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor/Angiotensin II Receptor Antagonist (AIIRA) therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3.) Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see sections 4.3 and 4.4).

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of the safety profile

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

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

	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count		Bone marrow failure, pancytopenia, haemolytic anaemia

			decreased, haemoglobin decreased, platelet count decreased		
Immune system disorders					Anaphylactic or anaphylactoid reactions, antinuclear antibody increased
Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite,			Blood sodium decreased
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Confusional state		Disturbance in attention
Nervous system disorders	Headache, dizziness	Vertigo, paraesthesia, ageusia, dysgeusia,	Tremor, balance disorder		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia
Eye disorders		Visual disturbance including blurred vision	Conjunctivitis		
Ear and labyrinth disorders			Hearing impaired, tinnitus		
Cardiac disorders		Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			
Vascular disorders	Hypotension, orthostatic blood pressure decreased, syncope	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation,	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE	Glossitis		Aphtous stomatitis

	digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth			
Hepatobiliary disorders		Hepatic enzymes and/or bilirubin conjugated increased,	Jaundice cholestatic, hepatocellular damage		Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional).
Skin and subcutaneous tissue disorders	Rash in particular maculo-papular	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Exfoliative dermatitis, urticaria, onycholysis,	Photosensitivity reaction	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia	Arthralgia			
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased			
Reproductive system and breast disorders		Transient erectile impotence, libido decreased			Gynaecomastia
General disorders and administration site conditions	Chest pain, fatigue	Pyrexia	Asthenia		

c) Paediatric Population

The safety of ramipril was monitored in 325 children and adolescents, aged 2-16 years old during 2 clinical trials. Whilst the nature and severity of the adverse events are similar to that of the adults, the frequency of the following is higher in the children:

- Tachycardia, nasal congestion and rhinitis, common (ie. ≥ 1/100 to < 1/10) in paediatric, and uncommon (i.e. ≥ 1/1,000 to < 1/100) in adult population.

- Conjunctivitis common (ie. ≥ 1/100 to < 1/10) in paediatric while rare (i.e. ≥ 1/10,000 to < 1/1,000) in adult population.
- Tremor and urticaria uncommon (ie. ≥ 1/1,000 to < 1/100) in paediatric population while rare (i.e. ≥ 1/10,000 to < 1/1,000) in adult population.

The overall safety profile for ramipril in paediatric patients does not differ significantly from the safety profile in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms associated with overdose of ACE inhibitors may include excessive peripheral vasodilation (with marked hypotension, shock), bradycardia, electrolyte disturbances and renal failure.

Management

The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including, administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 rennin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance. There is evidence suggesting that tissue 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.

Revascularisation procedures were performed in patients with an increased cardiovascular risk such as manifest coronary heart disease (with or without a history of myocardial infarction), a history of stroke, or a history of peripheral vascular disease. Revascularisation parameters showed a reduction in events versus placebo however the number of patients, particularly in non-cardiovascular interventions was small.

In patients with diabetes in association with at least one additional risk factor (microalbuminuria, hypertension, high cholesterol, low HDL cholesterol or current smoking), ramipril reduces the rate of diabetic complications (overt nephropathy, or the need for dialysis).

Paediatric Population
In a randomized, double-blind clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6-16 years, patients received either low dose, medium dose or high dose of ramipril to achieve plasma concentrations of ramiprilat corresponding to the adult dose range of 1.25 mg, 5 mg and 20 mg on the basis of body weight. At the end of 4

weeks, ramipril was ineffective in the endpoint of lowering systolic blood pressure but lowered diastolic blood pressure at the highest dose. Both medium and high doses of ramipril showed significant reduction of both systolic and diastolic BP in children with confirmed hypertension.

This effect was not seen in a 4 weeks dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6-16 years (75% primary hypertension), where both diastolic and systolic blood pressures demonstrated a modest rebound but not a statistically significant return to the baseline, in all three dose levels tested low dose (0.625 mg – 2.5 mg), medium dose (2.5 mg – 10 mg) or high dose (5mg – 20 mg) ramipril based on weight. Ramipril did not have a linear dose response in the paediatric population studied.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

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 ramiprilat are reached 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 5-10mg ramipril and markedly longer for lower doses, 1.25-2.5mg 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.

The protein binding of ramipril is about 73% and of ramiprilat about 50%.

Lactation:
One single 10 mg oral dose of ramipril produced an undetectable level in breast milk. However the effect of multiple doses is not known.

Paediatric Population
The pharmacokinetic profile of ramipril was studied in 30 paediatric hypertensive patients, aged 2-16 years, weighing ≥10 kg. After doses of 0.05 to 0.2 mg/kg, ramipril was rapidly and extensively metabolized to ramiprilat. Peak plasma concentrations of ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with the log of body weight ($p<0.01$) as well as dose ($p<0.001$). Clearance and volume of distribution increased with increasing children age for each dose group.

The dose of 0.05 mg /kg in children achieved exposure levels comparable to those in adults treated with ramipril 5mg. The dose of 0.2 mg/kg in children resulted in exposure levels higher than the maximum recommended dose of 10 mg per day in adults.

5.3 Preclinical safety data

Reproductive toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or female rats during the foetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50mg/kg body weight and higher.
Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Starch, pregelatinised

Capsules body and cap composition:
Titanium dioxide (E171)
Indigo carmine (E132)
Ponceau 4R (E124)
Black iron oxide (E172)
Gelatin
Water, purified
Sodium lauryl sulfate

Black printing ink:
Shellac
Anhydrous ethanol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Water, purified
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Alu/Alu Blisters

Pack sizes: 7, 21, 28, 30, 50 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0281/119/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2005

Date of last renewal: 10 June 2010

10 DATE OF REVISION OF THE TEXT

February 2020