SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 2.5 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ramipril 2.5 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard

Orange/White size ‘4’ hard gelatin capsules imprinted with ‘D’ on orange cap and ‘41’ on white body with black edible ink filled white to 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

Posology

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

Adults

Diuretic-Treated patients

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

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

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

Hypertension

The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control.

Ramipril may be used in monotherapy or in combination with other classes of antihypertensive medicinal products. (see Sections 4.3, 4.4, 4.5 and 5.1).

Starting dose

Ramipril should be started gradually with an initial recommended dose of 2.5 mg daily.

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

Titration and maintenance dose

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

Cardiovascular prevention

Starting dose

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

Titration and maintenance dose

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

See also posology on diuretic treated patients above.

Treatment of renal disease

In patients with diabetes and microalbuminuria:

Starting dose:

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

Titration and maintenance dose

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

In patients with diabetes and at least one cardiovascular risk

Starting dose:

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

Titration and maintenance dose

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

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

Starting dose:

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

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

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

Secondary prevention after acute myocardial infarction and with heart failure

Starting dose

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

See also posology on diuretic treated patients above.

Titration and maintenance dose

The daily dose is subsequently increased by doubling the dose at intervals of one to three days up to the target maintenance dose of 5 mg twice daily.

The maintenance dose is divided in 2 administrations per day where possible.

If the dose cannot be increased to 2.5 mg twice a day treatment should be withdrawn. Sufficient experience is still lacking in the treatment of patients with severe (NYHA IV) heart failure immediately after myocardial infarction. Should the decision be taken to treat these patients, it is recommended that therapy be started at 1.25 mg once daily and that particular caution be exercised in any dose increase.

Special populations

Patients with renal impairment

Daily dose in patients with renal impairment should be based on creatinine clearance (see section 5.2):

- If creatinine clearance is ≥ 60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 10 mg;
- If creatinine clearance is between 30-60 ml/min, it is not necessary to adjust the initial dose (2.5 mg/day); the maximal daily dose is 5 mg;
- If creatinine clearance is between 10-30 ml/min, the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg;
- In haemodialysed hypertensive patients: ramipril is slightly dialysable; the initial dose is 1.25 mg/day and the maximal daily dose is 5 mg; the medicinal product should be administered few hours after haemodialysis is performed.

Patients with hepatic impairment (see section 5.2)

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

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

Paediatric population

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.

Method of administration

Oral use

4.3 Contraindications

- Hypersensitivity to the ramipril, to any of the excipients listed in section 6.1 or any other ACE (Angiotensin Converting Enzyme) inhibitors

- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- Second and third trimester of pregnancy (see sections 4.4 and 4.6)
- Ramipril must not be used in patients with hypotensive or haemodynamically unstable states.
- The concomitant use of Ramipril 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).
- Concomitant use with sacubitril/valsartan therapy. Ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

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 inhibitor/ AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

- *Patients at particular risk of hypotension*

- *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 Section 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*

See section 4.2.

Surgery

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

Monitoring of renal function

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

Angioedema

Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of ramipril. Treatment with ramipril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (mammalian target of rapamycin) (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). in a patient already taking an ACE inhibitor

In case of angioedema, Ramipril must be discontinued.

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

Anaphylactic reactions during desensitization

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

Serum potassium

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Electrolyte Monitoring: Hyponatraemia

Syndrome of Inappropriate Antidiuretic 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 nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Excipients
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 interaction

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

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections 4.3 and 4.4). Treatment with ramipril must not be started until 36 hours after taking the last dose of sacubitril/valsartan. Sacubitril/valsartan must not be started until 36 hours after the last dose of Ramipril

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

Precautions for use

Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin):

Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics)

Vasopressor sympathomimetics and other substances (e.g. isoproterenol, dobutamine, dopamine, epinephrine) that may reduce the antihypertensive effect of ramipril.

Blood pressure monitoring is recommended.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count:

Increased likelihood of haematological reactions (see section 4.4).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with ramipril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when ramipril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of ramipril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

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

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

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

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

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

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

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Neprilysin (NEP) inhibitors:

An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and with NEP inhibitor such as racecadotril, (see section 4.4).

mTOR inhibitors

An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema. Caution should be used when starting therapy (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy:

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

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

Breast-feeding:

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

4.7 Effects on ability to drive and use machines

Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient’s ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).

This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Summary of 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.

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
Cardiac disorders		Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral			

Blood and lymphatic system disorders		Eosinophilia	White blood cell count decreased (including neutropenia or agranulocytosis) , red blood cell count decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anaemia
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		
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation, digestive	Pancreatitis (cases of fatal outcome	Glossitis		Aphtous stomatitis

	disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth			
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			

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			
Metabolism and nutrition disorders	Blood potassium increased	Anorexia, decreased appetite,			Blood sodium decreased
Vascular disorders	Hypotension, orthostatic blood pressure decreased, syncope	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon
General disorders and administration site conditions	Chest pain, fatigue	Pyrexia	Asthenia		
Immune system disorders					Anaphylactic or anaphylactoid reactions, antinuclear antibody increased

Endocrine disorders					Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
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).
Reproductive system and breast disorders		Transient erectile impotence, libido decreased			Gynaecomastia
Psychiatric disorders		Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Confusional state		Disturbance in attention

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 Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms

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

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

patients (usually a low-renin hypertensive population) than in non-black patients.

Pharmacodynamic effects

Antihypertensive properties:

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

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

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

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

Heart failure:

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

Clinical efficacy and safety

Cardiovascular prevention/Nephroprotection;

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

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

The HOPE study: Main results

	Ramipril	Placebo	relative risk (95% confidence interval)	p-value
	%	%		
All patients	**n=4,645**	**N=4,652**		
Primary combined events	**14.0**	**17.8**	**0.78 (0.70-0.86)**	**<0.001**
Myocardial infarction	*9.9*	*12.3*	*0.80 (0.70-0.90)*	*<0.001*
Death from cardiovascular causes	*6.1*	*8.1*	*0.74 (0.64-0.87)*	*<0.001*
Stroke	*3.4*	*4.9*	*0.68 (0.56-0.84)*	*<0.001*
Secondary endpoints				
Death from any cause	10.4	12.2	*0.84 (0.75-0.95)*	*0.005*
Need for Revascularisation	16.0	18.3	*0.85 (0.77-0.94)*	*0.002*
Hospitalisation for unstable angina	12.1	12.3	*0.98 (0.87-1.10)*	*NS*
Hospitalisation for heart failure	3.2	3.5	*0.88 (0.70-1.10)*	*0.25*
Complications related to diabetes	6.4	7.6	*0.84 (0.72-0.98)*	*0.03*

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

The primary analysis showed that 117 (6.5 %) participants on ramipril and 149 (8.4 %) on placebo developed overt nephropathy, which corresponds to a RRR 24 %; 95 % CI [3-40], p = 0.027. The REIN study, a multicenter randomized, double-blind parallel group, placebo-controlled study aimed at assessing the effect of treatment with ramipril on the rate of decline of glomerular function rate (GFR) in 352 normotensive or hypertensive patients (18-70 years old) suffering from mild (i.e. mean urinary protein excretion > 1 and < 3 g/24 h) or severe proteinuria (≥ 3 g/24 h) due to chronic non-diabetic nephropathy. Both subpopulations were prospectively stratified.

The main analysis of patients with the most severe proteinuria (stratum prematurely disrupted due to benefit in ramipril group) showed that the mean

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

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

Two large randomised, controlled trials (ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) have examined the use of 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. CV 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.

Secondary prevention after acute myocardial infarction

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

Paediatric Population

In a randomized, double-blind, placebo-controlled 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.

5.2 Pharmacokinetic properties

Pharmacokinetics and Metabolism

Absorption

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

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

Distribution

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

Biotransformation

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

Elimination

Excretion of the metabolites is primarily renal.

Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations.

After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat.

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

Patients with renal impairment (see section 4.2)

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

Patients with hepatic impairment (see section 4.2)

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

Lactation

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

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

Oral administration of ramipril has been found to be devoid of acute toxicity in rodents and dogs. Studies involving chronic oral administration have been conducted in rats, dogs and monkeys. Indications of plasma electrolyte shifts and changes in blood picture have been found in the 3 species. As an expression of the pharmacodynamic activity of ramipril, pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey from daily doses of 250 mg/kg/d.

Rats, dogs and monkeys tolerated daily doses of 2, 2.5 and 8 mg/kg/d respectively without harmful effects.

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties.

Fertility was not impaired either in male or in female rats.

The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.

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

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 Fill:

Hydrophobic colloidal anhydrous silica

Pregelatinized starch (maize)

Capsule Shell:

Gelatin

Sodium lauryl sulfate

Iron oxide yellow (E172)

Ponceau 4R (E124)

Titanium dioxide (E171)

Printing Ink:

Shellac

Propylene glycol

Black iron oxide (E172)

Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25° C.

Keep the blister in the outer carton. Keep the container tightly closed.

Store in the original package to protect from moisture.

6.5 Nature and contents of container

Ramipril capsules are available in Clear PVC/ PE/ PVdC- Aluminium blister pack and white opaque HDPE bottle pack.

Pack size:

Blister pack: 7, 10, 14, 20, 21, 28, 30, 42, 50, 56, 60, 90, 98 & 100 capsules

Bottle pack: 30, 100, 500 & 1000 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited

Ares, Odyssey Business Park

West End Road

South Ruislip HA4 6QD

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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