SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 2.5 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2.5 mg of ramipril.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
Opaque light orange cap and opaque white body hard gelatin capsules (No. 4), printed in black ink 93 and 7210 on opposing cap and body portions of the capsule.

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, 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 ≥ 3g/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

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.

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.

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

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**.**

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.

4.3 Contraindications

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

- 2nd and 3rd 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 m2) (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).

- *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.

Hypersensitivity/angioedema
Angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8).
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.
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 (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 in a patient already taking an ACE inhibitor.

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 and 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
Hyperkalaemia has been observed in some patients treated with ACE inhibitors including Ramipril. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, hypoaldosteronism, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis.
ACE inhibitors can cause hyperkalaemia 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, or other plasma potassium increasing active substances (e.g. heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalaemia 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).
If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

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 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

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 this medicinal product. 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 this medicinal product 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 this medicinal product 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.

Tacrolimus
Hyperkalaemia may occur, therefore close monitoring of serum potassium is required.

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

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).

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 effects 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.

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 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).

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

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

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.

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 decreased, haemoglobin decreased, platelet count decreased		Bone marrow failure, pancytopenia, haemolytic anemia
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 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,	Flushing	Vascular stenosis, hypoperfusion, vasculitis		Raynaud's phenomenon

	syncope				
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Bronchospasm including asthma aggravated, nasal congestion			
Gastrointestinal disorders	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema, abdominal pain upper including gastritis, constipation, dry mouth	Glossitis		Aphtous stomatitis
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		

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" (i.e. ≥ 1/100 to < 1/10) in paediatric, and "uncommon" (i.e. ≥ 1/1,000 to < 1/100) in adult population.
• Conjunctivitis "common" (i.e. ≥ 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" (.i.e. ≥ 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure. 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: C09A A05

Ramipril is a prodrug which, after absorption from the gastro-intestinal 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 as 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 ramipril 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.

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.

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.

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, ramipirlat, 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 this dose indicating a saturable capacity of the enzyme to bind ramiprilat. Steady-state plasma concentrations of ramiprilat after once daily dosing with the usual dose 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.

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 5 mg. 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.

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.

5.3 Preclinical safety data

Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

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. The administration of ramipril to female rats during the foetal period and lactation produced irreversible renal damage (dilation 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
Calcium hydrogen phosphate
Magnesium Hydroxide
Colloidal anhydrous silica
Magnesium Stearate
Talc

Capsule shell:
Red Iron Oxide (E172)
Yellow Iron Oxide (E172)

Titanium Dioxide (E171)
Gelatin

Ink:
Shellac
Propylene Glycol
Potassium Hydroxide
Black Iron Oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

15 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Transparent PVC/Aclar® (254 µm-51 µm) - aluminium blisters and transparent PVC/PE/PVdC(PVC 250µm thick; PE 25µm; PVdC coating 120g/m2) aluminium blisters containing 28 or 30 capsules, or 50 capsules in EAV (unit dose hospital pack) blisters.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
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8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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