SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<[Invented name]> 2.5 mg/5 mg, hard capsule
<[Invented name]> 5 mg/5 mg, hard capsule
<[Invented name]> 10 mg/5 mg, hard capsule
<[Invented name]> 5 mg/10 mg, hard capsule
<[Invented name]> 10 mg/10 mg, hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<[Invented name]> 2.5 mg/5 mg: Each capsule contains 2.5 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.

<[Invented name]> 5 mg/5 mg: Each capsule contains 5 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.

<[Invented name]> 10 mg/5 mg: Each capsule contains 10 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.

<[Invented name]> 5 mg/10 mg: Each capsule contains 5 mg ramipril and amlodipine besilate equivalent to 10 mg amlodipine.

<[Invented name]> 10 mg/10 mg: Each capsule contains 10 mg ramipril and amlodipine besilate equivalent to 10 mg amlodipine.

Excipient with known effect: sodium.
<[Invented name]>: Each capsule contains 0.26 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

<[Invented name]> 2.5 mg/5 mg: Hard gelatin capsules, size no.1, cap: opaque pale pink colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 5 mg/5 mg: Hard gelatin capsules, size no.1, cap: opaque pink colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 10 mg/5 mg: Hard gelatin capsules, size no.1, cap: opaque dark pink colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 5 mg/10 mg: Hard gelatin capsules, size no.1, cap: opaque red-brown colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 10 mg/10 mg: Hard gelatin capsules, size no.1, cap: opaque brown colour, body: opaque white colour. Content of capsules: white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension in adults.

<[Invented name]> is indicated as substitution therapy of patients with blood pressure adequately controlled with ramipril and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration

Posology

<[Invented name]> should not be used for initiating treatment of hypertension. The doses of each component should be individualised according to the patient profile and blood pressure control.

If a dose change is required, the dosing regimen should be individually determined using the individual components of ramipril and amlodipine first, and once established, it could be changed to <[Invented name]>.

The recommended dose is one capsule daily. The maximum daily dose is one capsule 10 mg/10 mg.

Special populations

Renal impairment

To find the optimal starting dose and maintenance dose of patients with renal impairment, the patients should be individually titrated using the individual components of amlodipine and ramipril.

Ramipril is slightly dialysable, the medicinal product should be administered few hours after haemodialysis is performed.

Amlodipine is not dialysable. Amlodipine should be administered with particular caution to patients undergoing dialysis.

Renal function and serum potassium levels should be monitored during therapy with <[Invented name]>. In the case of renal function deterioration, the use of <[Invented name]> should be discontinued and replaced by the individual components adequately adjusted.

Hepatic impairment

The maximum daily dose is 2.5 mg ramipril.

Elderly

Lower initial dosage is recommended in the elderly and increase of the dosage should take place with care.

Paediatric population

The safety and efficacy of <[Invented name]> in children has not been established.

Currently available data are described in section 4.8, 5.1, 5.2 and 5.3 but no recommendation on a posology can be made.

Method of administration

Since food does not affect absorption of ramipril and amlodipine, <[Invented name]> may be taken irrespective of meals. It is recommended that <[Invented name]> is taken at the same time of the day.

4.3 Contraindications

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

Related to ramipril

- The concomitant use of <[Invented name]> with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2) (see sections 4.5 and 5.1).
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or angiotensin II receptor antagonists).
- Concomitant use with sacubitril/valsartan therapy (see section 4.4 and 4.5).
- 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 trimesters of pregnancy (see sections 4.4 and 4.6).
- Hypotensive or haemodynamically unstable states.

Related to amlodipine

- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

Caution is recommended in patients who are being treated concurrently with diuretics since these patients may be volume and/or salt depleted. Renal function and serum potassium should be monitored.

Related to ramipril

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.

Special populations

Pregnancy

ACE inhibitors should not be initiated during pregnancy. 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 (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 myocardial infarction.
- 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). This risk of angioedema may be increased in patients taking concomitant medications which may cause angioedema such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril).

The combination of ramipril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections 4.3 and 4.5).

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.

Electrolyte monitoring: Hyperkalaemia

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, 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: Hyponatremia

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatremia 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 hyponatremia.

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 isnon-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Related to amlodipine

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Special populations

Heart failure

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Hepatic impairment

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly

In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

Renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Warning about excipients

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

Related to ramipril

Contra-indicated combinations

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 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 <[Invented name]>.

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.

<u>*Precautions for use*</u>

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

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).

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, cyclosporine)

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, 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.

mTOR inhibitors or vildagliptin

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).

Neprilysin (NEP) inhibitors

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

<u>Related to amlodipine</u>

<u>*Effects of other medicinal products on amlodipine*</u>

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Close clinical observation of patients is recommended and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

<u>*Effects of amlodipine on other medicinal products*</u>

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0 – 40%) of cyclosporine were observed.

Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

4.6 Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation

<[Invented name]> is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy.

<[Invented name]> is not recommended during lactation. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with <[Invented name]> should be made taking into account the benefit of breastfeeding to the child and the benefit of amlodipine therapy to the mother.

Pregnancy

Related to ramipril

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 trimesters of pregnancy (see sections 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 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).

Related to amlodipine

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

Related to ramipril

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.

Related to amlodipine

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

<[Invented name]> can have minor or moderate influence on the ability to drive and use machines. Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness, headache, fatigue) 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. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

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

The most commonly reported adverse reactions during treatment with amlodipine are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

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).

The following adverse drug reactions have been reported during the treatment with ramipril and amlodipine independently:

System organ class	**Frequency**	**Ramipril**	**Amlodipine**
Blood and lymphatic system disorders	Uncommon	Eosinophilia	
	Rare	White blood cell count decreased (including neutropenia or agranulocytosis), red blood cell count decreased, haemoglobin decreased, platelet count decreased	
	Very rare		Leukocytopenia, thrombocytopenia
	Not known	Bone marrow failure, pancytopenia, haemolytic anaemia	
Immune system	Very rare		Allergic reactions

disorders	Not known	Anaphylactic or anaphylactoid reactions, antinuclear antibody increased	
Endocrine disorders	Not known	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
Metabolism and nutrition disorders	Common	Blood potassium increased	
	Uncommon	Anorexia, decreased appetite	
	Very rare		Hyperglycaemia
	Not known	Blood sodium decreased	
Psychiatric disorders	Uncommon	Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	Insomnia, mood changes (including anxiety), depression
	Rare	Confusional state	Confusion
	Not known	Disturbance in attention	
Nervous system disorders	Common	Headache, dizziness	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Vertigo, paraesthesia, ageusia, dysgeusia	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
	Rare	Tremor, balance disorder	
	Very rare		Hypertonia peripheral neuropathy
	Not known	Cerebral ischemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia	Extrapyramidal disorder
Eye disorders	Common		Visual disturbance (including diplopia)

	Uncommon	Visual disturbance including blurred vision	
	Rare	Conjunctivitis	
Ear and labyrinth disorders	Uncommon		Tinnitus
	Rare	Hearing impaired, tinnitus	
Cardiac disorders	Common		Palpitations
	Uncommon	Myocardial ischemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, Oedema peripheral	Arrhythmia, (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare		Myocardial infarction
Vascular disorders	Common	Hypotension, orthostatic blood pressure decreased, syncope	Flushing
	Uncommon	Flushing	Hypotension
	Rare	Vascular stenosis, hypoperfusion, vasculitis	
	Very rare		Vasculitis
	Not known	Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders	Common	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	Dyspnoea
	Uncommon	Bronchospasm including asthma aggravated, nasal congestion	Cough, rhinitis
Gastrointestinal disorders	Common	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema,	Vomiting, dry mouth

		abdominal pain upper including gastritis, constipation, dry mouth	
	Rare	Glossitis	
	Very rare		Pancreatitis, gastritis, gingival hyperplasia
	Not known	Aphtous stomatitis	
Hepatobiliary disorders	Uncommon	Hepatic enzymes and/or bilirubin conjugated increased	
	Rare	Jaundice cholestatic, hepatocellular damage	
	Very rare		Hepatitis, jaundice, hepatic enzymes increased*
	Not known	Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional)	
Skin and subcutaneous tissue disorders	Common	Rash in particular maculo-papular	
	Uncommon	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema urticaria
	Rare	Exfoliative dermatitis, urticaria, onycholysis,	
	Very rare	Photosensitivity reaction	Angioedema, erythema, multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis	Toxic epidermal necrolysis

		aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia	
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, myalgia	Ankle swelling, muscle cramps
	Uncommon	Arthralgia	Arthralgia, myalgia back pain
Renal and urinary disorders	Uncommon	Renal impairment including renal failure acute, urine output increased, worsening of a pre-existing proteinuria, blood urea increased, blood creatinine increased	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Transient erectile impotence, libido decreased	Impotence, gynaecomastia
	Not known	Gynaecomastia	
General disorders and administration site conditions	Very common		Oedema
	Common	Chest pain, fatigue	Fatigue, asthenia
	Uncommon	Pyrexia	Chest pain, pain, malaise
	Rare	Asthenia	
Investigations	Uncommon		Weight increased, weight decreased

* Mostly consistent with cholestasis.

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 national reporting system listed in Appendix V, <[To be completed nationally]>.

4.9 Overdose

Related to ramipril

Symptoms

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (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.

<u>Related to amlodipine</u>

In humans experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Management

Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: an angiotensin-converting enzyme inhibitor and calcium channel blocker; ATC code: C09 BB07.

<u>Related to ramipril</u>

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.

Clinical efficacy and safety

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.

Cardiovascular prevention

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).

Table 1. 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 $\geq$ 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.

Paediatric population

In a randomized, double-blind, placebo-controlled clinical study involving 244 paediatric patients with hypertension (73% primary hypertension), aged 6 to 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 blood pressure in children with confirmed hypertension.

This effect was not seen in a 4 week dose-escalation, randomized, double-blind withdrawal study in 218 paediatric patients aged 6 to 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 (5 mg – 20 mg)] ramipril based on weight. Ramipril did not have a linear dose response in the paediatric population studied.

Related to amlodipine

Mechanism of action

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with heart failure

Long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5 – 10 mg/d (calcium channel blocker) or lisinopril 10 – 40 mg/d (ACE inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5 – 25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrolment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90 – 1.07) p = 0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% % vs. 7.7%, RR 1.38, 95% CI [1.25 – 1.52] p < 0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89 – 1.02] p = 0.20.

Paediatric population (aged 6 years and older)

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

The European Medicines Agency has waived the obligation to submit the results of studies with <[Invented name]> in all subsets of the paediatric population in the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Related to ramipril

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.

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. These results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

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

One single 10mg 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 to16 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.

<u>Related to amlodipine</u>

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6 – 12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 L/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40 – 60%.

Elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Paediatric population

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13 to 17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3 Preclinical safety data

Related to ramipril

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 foetal 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.

Related to amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis).

In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Capsule content</u>

Cellulose, microcrystalline

Calcium hydrogen phosphate, anhydrous

Maize starch, pregelatinised

Sodium starch glycolate (type A)

Sodium stearyl fumarate

<[Invented name]> 2.5 mg/5 mg; 5 mg/5 mg; 10 mg/5 mg; 5 mg/10 mg:

<u>Capsule shell</u>

Iron oxide red (E172)

Titanium dioxide (E171)

Gelatin

<[Invented name]> 10 mg/10 mg:

<u>Capsule shell</u>

Iron oxide yellow (E172)

Iron oxide black (E172)
Iron oxide red (E172)
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

<[Invented name]> 2.5 mg/5 mg: 2 years
<[Invented name]> 5 mg/5 mg, 10 mg/5 mg, 5 mg/10 mg, 10 mg/10 mg: 30 months

6.4 Special precautions for storage

Store below 30 °C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

PA/Aluminium/PVC/Aluminium blisters.
Pack sizes: 28, 30, 32, 56, 60, 90, 91, 96, 98, 100 hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: <[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

<[Invented name]> 2.5 mg/5 mg, hard capsule
<[Invented name]> 5 mg/5 mg, hard capsule
<[Invented name]> 10 mg/5 mg, hard capsule
<[Invented name]> 5 mg/10 mg, hard capsule
<[Invented name]> 10 mg/10 mg, hard capsule

ramipril/amlodipine

2. STATEMENT OF ACTIVE SUBSTANCES

Each capsule contains 2.5 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.
Each capsule contains 5 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.
Each capsule contains 10 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.
Each capsule contains 5 mg ramipril and amlodipine besilate equivalent to 10 mg amlodipine.
Each capsule contains 10 mg ramipril and amlodipine besilate equivalent to 10 mg amlodipine.

3. LIST OF EXCIPIENTS

Contains sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

28 hard capsules
30 hard capsules
32 hard capsules,
56 hard capsules
60 hard capsules
90 hard capsules
91 hard capsules
96 hard capsules
98 hard capsules
100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<[Invented name]> 2.5 mg/5 mg, hard capsule
<[Invented name]> 5 mg/5 mg, hard capsule
<[Invented name]> 10 mg/5 mg, hard capsule
<[Invented name]> 5 mg/10 mg, hard capsule
<[Invented name]> 10 mg/10 mg, hard capsule

17. UNIQUE IDENTIFIER – 2D BARCODE*

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

<[Invented name]> 2.5 mg/5 mg, hard capsule
<[Invented name]> 5 mg/5 mg, hard capsule
<[Invented name]> 10 mg/5 mg, hard capsule
<[Invented name]> 5 mg/10 mg, hard capsule
<[Invented name]> 10 mg/10 mg, hard capsule

ramipril/amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Package leaflet: information for the patient

<[Invented name]> 2.5 mg/5 mg, hard capsule
<[Invented name]> 5 mg/5 mg, hard capsule
<[Invented name]> 10 mg/5 mg, hard capsule
<[Invented name]> 5 mg/10 mg, hard capsule
<[Invented name]> 10 mg/10 mg, hard capsule
Ramipril/amlodipine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What <[Invented name]> is and what it is used for
2. What you need to know before you take <[Invented name]>
3. How to take <[Invented name]>
4. Possible side effects
5. How to store <[Invented name]>
6. Contents of the pack and other information

1. What <[Invented name]> is and what it is used for

<[Invented name]> contains two active substances: ramipril and amlodipine. Ramipril belongs to a group of medicines called ACE inhibitors (Angiotensin Converting Enzyme inhibitors). Amlodipine belongs to a group of medicines called calcium antagonists.

Ramipril works by:
- Decreasing your body’s production of substances that could raise your blood pressure.
- Making your blood vessels relax and widen.
- Making it easier for your heart to pump blood around your body.

Amlodipine works by:

- Relaxing and widening blood vessels, so that blood passes through them more easily.

<[Invented name]> is used to treat hypertension (high blood pressure), in patients whose blood pressure is adequately controlled with amlodipine and ramipril given concurrently at the same dose level as in <[Invented name]>, but as a separate medicines.

2. What you need to know before you take <[Invented name]>

Do not take <[Invented name]>

- if you are allergic to ramipril, amlodipine (active substances), other ACE inhibitor medicines or any other calcium antagonists, or any of the other ingredients of this medicine (listed in section 6). Signs of an allergic reaction may include a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- If you have ever had a serious allergic reaction called "angioedema". The signs include itching, hives (urticaria), red marks on the hands, feet and throat, swelling of the throat and tongue, swelling around the eyes and lips, difficulty breathing and swallowing.
- If you have taken or are currently taking sacubitril/valsartan, a medicine used to treat a type of long-term (chronic) heart failure in adults. Tell your doctor or pharmacist if you are using, have recently taken or might take sacubitril/valsartan.
- If you are having dialysis or any other type of blood filtration. Depending on the machine that is used, <[Invented name]> may not be suitable for you.
- If you have kidney problems where the blood supply to your kidneys is reduced (renal artery stenosis).
- During the last 6 months of pregnancy (see section below on "Pregnancy, breast-feeding and fertility").
- If you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.
- If your blood pressure is abnormally low or unstable. Your doctor will need to make this assessment.
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack.

Do not take <[Invented name]> if any of the above apply to you. If you are not sure, talk to your doctor before taking <[Invented name]>.

Warnings and precautions

Talk to your doctor or pharmacist before taking <[Invented name]>. Tell your doctor, if any of the situations listed below is applicable to you:

- If you have heart, liver or kidney problems.
- If you have lost a lot of body salts or fluids (through being sick (vomiting), having diarrhoea, sweating more than usual, being on a low salt diet, taking diuretics (water tablets) for a long time or having had dialysis).
- If you are going to have treatment to reduce your allergy to bee or wasp stings (desensitization).
- If you are going to receive an anesthestic. This may be given for an operation or any dental work. You may need to stop your <[Invented name]> treatment one day beforehand; ask your doctor for advice.
- If you have high amounts of potassium in your blood (shown in blood test results).
- If you are taking medicines or have conditions which may decrease sodium levels in your blood. Your doctor may carry out regular blood tests, particularly for checking the levels of sodium in your blood especially if you are elderly.
- If you are taking medicines that may increase the risk of angioedema, a serious allergic reaction, such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril).
- If you have a collagen vascular disease such as scleroderma or systemic lupus erythematosus.
- You must tell your doctor if you think that you are (or might become) pregnant. <[Invented name]> is not recommended in the first 3 months of pregnancy and may cause serious harm to your baby after 3 months of pregnancy (see section below on “Pregnancy and breast-feeding”).
- if you are taking any of the following medicines used to treat high blood pressure:
    - An angiotensin II receptor blocker (ARBs) (also known as sartans – for example valsartan, telmisartan, irbesartan), in particular if you have diabetes-related kidney problems.
    - Aliskiren

Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

See also information under the heading “Do not take <[Invented name]>”.

- If you had severe increase in blood pressure (hypertensive crisis).
- If you are elderly and your dose needs to be increased.
- If you developed a dry cough which is persistent for a long time.
- if your blood pressure is not sufficiently lowered. Medicines of this type seem to be less effective in persons with black skin.

If you suffer from sudden swelling of the lips and face, tongue and throat, neck, possibly also hands and feet, difficulty to swallow or to breathe, hives or hoarseness (“angioedema”). This could be a sign of a severe allergic reaction. This may occur at any time during the treatment. Persons with black skin may have a higher risk of suffering from this condition. If you develop such symptoms you should let your doctor know immediately.

Children and adolescents

<[Invented name]> is not recommended for use in children and adolescents below 18 years of age because there is no information available in this population.

Other medicines and <[Invented name]>

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines. They can make <[Invented name]> work less well:

- Medicines used to relieve pain and inflammation (e.g. on-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indomethacin and aspirin)
- Medicines used for the treatment of low blood pressure, shock, cardiac failure, asthma or allergies such as ephedrine, noradrenaline or adrenaline. Your doctor will need tocheck your blood pressure.
- *Hypericum perforatum* (St. John's Wort use to treat depression).

Tell your doctor if you are taking any of the following medicines. They can increase the chance of getting side effects if you take them with <[Invented name]>. Your doctor may need to change your dose and/or to take other precautions:

- Sacubitril/valsartan - used for treating a type of long-term (chronic) heart failure in adults (see also information under the headings "Do not take <[Invented name]>")
- Medicines used to relieve pain and inflammation (e.g. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen or indomethacin and acetylsalicylic acid).
- Medicines for cancer (chemotherapy).
- Medicines to stop the rejection of organs after a transplant such as cyclosporine.
- Diuretics (water tablets) such as furosemide.
- An angiotensin II receptor blocker (ARB) or aliskiren (see also information under the headings "Do not take <[Invented name]>" and "Warnings and precautions").
- Medicines which can increase the amount of potassium in your blood such as spironolactone, triamterene, amiloride, potassium salts and heparin (for thinning blood).
- Steroid medicines for inflammation such as prednisolone.
- Allopurinol (used to lower the uric acid in your blood).
- Procainamide (for heart rhythm problems).
- Temsirolimus (for cancer).
- Sirolimus, everolimus (for prevention of graft rejection).
- Vildagliptin (used for treating type 2 diabetes).
- Racecadotril (used against diarrhoea).
- Ketoconazole, itraconazole (anti-fungal medicines).

– Ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV).
– Rifampicin, erythromycin, clarithromycin (antibiotics - for infections caused by bacteria).
– Trimethoprim and co-trimoxazole (for infections caused by bacteria).
– Verapamil, diltiazem (medicines to treat heart disorders or high blood pressure).
– Dantrolene (infusion for severe body temperature abnormalities).
– Tacrolimus (used to control your body's immune response, enabling your body to accept the transplanted organ).
– Simvastatin (cholesterol lowering medicine).

Please tell your doctor if you are taking any of the following medicines. They may be affected by <[Invented name]>:

– Medicines for diabetes such as oral, glucose lowering medicines and insulin. <[Invented name]> may lower your blood sugar amounts. Check your blood sugar amounts closely while taking <[Invented name]>.
– Lithium (for mental health problems). <[Invented name]> may increase the amount of lithium in your blood. Your lithium amount will need to be closely checked by your doctor.
– Simvastatin (a cholesterol lowering medicine). <[Invented name]> may increase the amount of simvastatin in your blood.

If any of the above apply to you (or you are not sure), talk to your doctor before taking <[Invented name]>.

<[Invented name]> with food, drink and alcohol

<[Invented name]> may be taken with or without food.

Drinking alcohol with <[Invented name]> may make you feel dizzy or light-headed. If you are concerned about how much you can drink while you are taking <[Invented name]>, discuss this with your doctor as medicines used to reduce blood pressure and alcohol can have additive effects.

Grapefruit juice or grapefruit should not be consumed by people who are taking <[Invented name]>. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of <[Invented name]>.

Pregnancy and breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You should not take <[Invented name]> in the first 12 weeks of pregnancy and you must not take <[Invented name]> at all after the 13th week as its use during pregnancy may possibly be harmful to the baby. If you become pregnant while on <[Invented name]>, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

Breast-feeding

Amlodipine has been shown to pass into breast milk in small amounts.

You should not take <[Invented name]> if you are breastfeeding.

You should talk to your doctor or pharmacist before taking any medicine.

Fertility

There is no sufficient data regarding the potential effect on fertility.

Driving and using machines

<[Invented name]> may affect your ability to drive or use machines. If the <[Invented name]> make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately. This can happen especially at the start of treatment, or when changing over from other preparations.

<[Invented name]> contains sodium

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

3. How to take <[Invented name]>

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you have the impression that the effect of <[Invented name]> is too strong or too weak, talk to your doctor or pharmacist.

Take this medicine by mouth at the same time of the day, before or after your meal.

Swallow the whole capsule with liquid.

Do not take <[Invented name]> with grapefruit juice.

<[Invented name]> should be administered once a day.

The doctor may modify the dose, depending on the effect it will have on you.

The maximum daily dose is one capsule 10 mg/10 mg.

Elderly

Your doctor will reduce the initial dose and adjust your treatment more slowly.

Use in children and adolescents

<[Invented name]> is not recommended for use in children and adolescents below 18 years of age because there is no information available in this population.

If you take more <[Invented name]> than you should

Taking too many capsules may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Tell a doctor or go to the nearest hospital casualty department straight away. Do not drive to the hospital, get somebody else to take you or call for an ambulance. Take the medicine pack with you. This is so the doctor knows what you have taken.

If you forget to take use <[Invented name]>

If you forget to take a capsule, leave out that dose completely. Take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking <[Invented name]>

Your doctor will advise you how long to take your medicine. Your condition may return if you stop using your medicine before you are advised.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking <[Invented name]> and see a doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment:

- Swelling of the face, lips or throat which make it difficult to swallow or breathe, as well as itching and rashes. This could be a sign of a severe allergic reaction to <[Invented name]>.
- Severe skin reactions including rash, ulcers in your mouth, worsening of a pre-existing skin disease, reddening, blistering or detachment of skin (such as Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiform) or other allergic reactions.

The frequencies of the above mentioned side effects are classified as not known (cannot be estimated from the available data)

Tell your doctor immediately if you experience:

– Faster heart rate, uneven or forceful heartbeat (palpitations), chest pain, tightness in your chest or more serious problems including heart attack and stroke.
– Shortness of breath or a cough. These could be signs of lung problems.
– Bruising more easily, bleeding for longer than normal, any sign of bleeding (e.g. bleeding from the gums), purple spots, blotching on the skin or getting infections more easily than usual, sore throat and fever, feeling tired, faint, dizzy or having pale skin. These can be signs of blood or bone marrow problems.
– Severe stomach pain which may reach through to your back. This could be a sign of pancreatitis (inflammation of the pancreas).
– Fever, chills, tiredness, loss of appetite, stomach pain, feeling sick, yellowing of your skin or eyes (jaundice). These can be signs of liver problems such as hepatitis (inflammation of the liver) or liver damage.

Other side effects include:

Tell your doctor if any of the following gets serious or lasts longer than a few days.

Very common: may affect more than 1 in 10 people

– Ankle swelling (oedema).

Common (may affect up to 1 in 10 people):

– Sleepiness (especially at the beginning of treatment).
– Palpitations (awareness of your heart beat), flushing.
– Headache or feeling tired, weakness.
– Feeling dizzy. This is more likely to happen when you start taking <[Invented name]> or start taking a higher dose.
– Fainting, hypotension (abnormally low blood pressure), especially when you stand or sit up quickly.
– Dry tickly cough, inflammation of your sinuses (sinusitis) or bronchitis, shortness of breath.
– Abdominal pain, stomach or gut pain, altered bowel habits (including diarrhoea or constipation), indigestion, feeling or being sick.
– Skin rash with or without raised area.
– Chest pain.
– Visual disturbances, double vision.
– Cramps or pain in your muscles.
– Blood tests showing more potassium than usual in your blood.

Uncommon (may affect up to 1 in 100 people):

– Mood changes, sleeplessness.
– Trembling, feeling unwell.

– Blurred vison.
– Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis).
– Heartburn, dry mouth.
– Hair loss, increased sweating, itchy skin, red patches on skin, skin discoloration.
– Disorder in passing urine, increased need to urinate, especially at night, increased number of times of passing urine.
– Inability to obtain an erection, sexual inability in men, reduced sexual desire in men or women.
– Discomfort or enlargement of the breasts in men.
– Joint or muscle pain, back pain.
– Weight increase or decrease.
– Balance problems (vertigo).
– Itching and unusual skin sensations such as numbness, tingling, pricking, burning or creeping on your skin (paraesthesia), loss of pain sensation.
– Loss or change in the way things taste.
– Sleep problems.
– Feeling depressed, anxious, more nervous than usual or restless.
– Blocked nose, difficulty breathing or worsening of asthma.
– A swelling in your gut called "intestinal angioedema" presenting with symptoms like abdominal pain and vomiting.
– Loss or decrease of appetite (anorexia).
– Increased or irregular heart beats.
– Swollen arms and legs. This may be a sign of your body holding onto more water than usual.
– Fever.
– An increased number of certain white blood cells (eosinophilia) found during a blood test.
– Blood tests showing changes in the way your liver, pancreas or kidneys are working.

Rare (may affect up to 1 in 1,000 people)
– Feeling shaky or confused.
– Red and swollen tongue.
– Severe flaking or peeling skin, itchy, lumpy rash.
– Nail problems (e.g. loosening or separation of a nail from its bed).
– Skin rash or bruising.
– Urticaria.
– Blotches on your skin and cold extremities.
– Red, itchy, swollen or watery eyes.
– Disturbed hearing and ringing in your ears.
– Blood tests showing a decrease in the number of red blood cells, white blood cells or platelets or in the amount of haemoglobin.

Very rare (may affect up to 1 in 10,000 people)

- Being more sensitive to the sun than usual.
- Excess sugar in blood (hyperglycaemia).
- Swelling of the gums.
- Abdominal bloating (gastritis).
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension.
- Inflammation of blood vessels, often with skin rash.
- Sensitivity to light.
- Disorders combining rigidity, tremor, and/or movement disorders.
- A disorder of the nerves which can cause weakness, tingling or numbness (peripheral neuropathy).

Not known (frequency cannot be estimated from from the available data)

- Concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion. If you have these symptoms contact your doctor as soon as possible.
- Trembling, rigid posture, mask-like face, slow movements and a shuffling, unbalanced walk.

Other side effects reported:

Please tell your doctor if any of the following gets serious or lasts longer than a few days.

- Difficulty concentrating.
- Swollen mouth.
- Blood tests showing too few blood cells in your blood.
- Blood tests showing less sodium than usual in your blood.
- Fingers and toes changing colour when you are cold and then tingling or feeling painful when you warm up (Raynaud's phenomenon).
- Slowed or impaired reactions.
- Change in the way things smell.
- Psoriasis.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <[Invented name]>

Store below 30 °C.
Store in the original package in order to protect from light.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister pack after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What <[Invented name]> contains

- The active substances are:

  <[Invented name]> 2.5 mg/5 mg: Each capsule contains 2.5 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.

  <[Invented name]> 5 mg/5 mg: Each capsule contains 5 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.

  <[Invented name]> 10 mg/5 mg: Each capsule contains 10 mg ramipril and amlodipine besilate equivalent to 5 mg amlodipine.

  <[Invented name]> 5 mg/10 mg: Each capsule contains 5 mg ramipril and amlodipine besilate equivalent to 10 mg amlodipine.

  <[Invented name]> 10 mg/10 mg: Each capsule contains 10 mg ramipril and amlodipine besilate equivalent to 10 mg amlodipine.
- The other ingredients are: cellulose microcrystalline, calcium hydrogen phosphate, anhydrous, mazize starch, pregelatinised, sodium starch glycolate (type A), sodium stearyl fumarate, iron oxide red (E 172), titanium dioxide (E 171), gelatine, iron oxide yellow (E 172) (10 mg/10 mg), iron oxide black (E 172) (10 mg/10 mg)

What <[Invented name]> looks like and contents of the pack

<[Invented name]> 2.5 mg/5 mg: Hard gelatine capsules, cap: opaque pale pink colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 5 mg/5 mg: Hard gelatine capsules, cap: opaque pink colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 10 mg/5 mg: Hard gelatine capsules, cap: opaque dark pink colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 5 mg/10 mg: Hard gelatine capsules, cap: opaque red - brown colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> 10 mg/10 mg: Hard gelatine capsules, cap: opaque brown colour, body: opaque white colour. Content of capsules: white or almost white powder.

<[Invented name]> is available in blister packs containing 28, 30, 32, 56, 60, 90, 91, 96, 98 or 100 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

<[To be completed nationally]>

Manufacturer

<[To be completed nationally]>

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

Slovak Republic	Ramipril/Amlodipin Sanofi
Czech Republic	Tritace Combi
Poland	Amrap
Bulgaria	Tritace combo
Italy, Greece, Cyprus	Triamlo

This leaflet was last revised in {MM/YYYY}

<[To be completed nationally]>