SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Invented name] 5 mg/1.25 mg, capsules, hard
[Invented name] 5 mg/2.5 mg, capsules, hard
[Invented name] 10 mg/1.25 mg, capsules, hard
[Invented name] 10 mg/2.5 mg, capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Invented name] 5 mg/1.25 mg:	Each capsule hard contains 5 mg ramipril and 1.25 mg indapamide.
[Invented name] 5 mg/2.5 mg:	Each capsule hard contains 5 mg ramipril and 2.5 mg indapamide.
[Invented name] 10 mg/1.25 mg:	Each capsule hard contains 10 mg ramipril and 1.25 mg indapamide.
[Invented name] 10 mg/2.5 mg:	Each capsule hard contains 10 mg ramipril and 2.5 mg indapamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard

[Invented name] 5 mg/1.25 mg: Hard gelatin yellow capsules, with overprint on the body 5+1,25; size of capsules - no. 3 (approximately 16 mm in length), containing a filling in the form of a white or almost white powder or slightly compacted larger agglomerates.
[Invented name] 5 mg/2.5 mg: Hard gelatin capsules, yellow body, orange cap, with overprint on the body 5 mg+2,5 mg; size of capsules - no.1 (approximately 19.5 mm in length), containing a filling in the form of a white or almost white powder or slightly compacted larger agglomerates.
[Invented name] 10 mg/1.25 mg: Hard gelatin capsules, orange body, red cap, with overprint on the body 10 mg+1,25 mg; size of capsules - no. 1 (approximately 19.5 mm in length), containing a filling in the form of a white or almost white powder or slightly compacted larger agglomerates.
[Invented name] 10 mg/2.5 mg: Hard gelatin red capsules, with overprint on the body 10 mg+2,5 mg; size of capsules - no. 1 (approximately 19.5 mm in length), containing a filling in the form of a white or almost white powder or slightly compacted larger agglomerates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled by the use of ramipril and indapamide given concurrently at the same dose level as in the combination, but as separate medicinal products.

4.2 Posology and method of administration

Posology

Adults
Recommended daily dose is one capsule of the given strength.

The fixed dose combination is not suitable for initial therapy.
Before switching to [Invented name] patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of [Invented name] should be based on the doses of the individual components of the combination at the time of switching.

If the change of posology is required for any of the active substances of the fixed combination due to any reason (e.g. newly diagnosed related illness, change of the condition of the patient or due to drug interaction), the individual components should be used again in order to determine the posology.

Special populations
Patients with hepatic impairment (see sections 4.3 and 4.4)
In severe hepatic impairment, treatment is contraindicated.

Patients with renal impairment
In severe renal impairment (creatinine clearance below 30 ml/min), treatment is contra-indicated.
In patients with moderate renal impairment (creatinine clearance 30-60 ml/min), it is recommended to start treatment with the adequate dosage of the free combination.
In patients with creatinine clearance greater than or equal to 60 ml/min, no dose modification is required.
Usual medical follow-up will include frequent monitoring of creatinine and potassium.

Elderly (*see section 4.4*)
Treatment should be initiated after considering blood pressure response and renal function.

Paediatric population
Ramipril and indapamide is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Method of administration
Oral use.
[Invented name] may be taken once daily, preferably to be taken in the morning with a sufficient amount of fluid (e.g. on glass of water).

4.3 Contraindications

- Hypersensitivity to the active substances or to other ACE inhibitors, or to other sulphonamides, 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
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- Lactation (see section 4.6)
- [Invented name] must not be used in patients with hypotensive or haemodynamically unstable states
- The concomitant use of [Invented name] with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) (see sections 4.5 and 5.1)
- Concomitant use with sacubitril/valsartan therapy. Ramipril must not be initiated earlier than

36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5)
- Severe renal failure (creatinine clearance below 30 ml/min)
- Hepatic encephalopathy or severe impairment of liver function
- Hypokalaemia.

Due to the lack of sufficient therapeutic experience, [Invented name] should not be used in:
- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Linked to ramipril

Special populations

- *Pregnancy*

ACE inhibitors such as ramipril 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 MI*

- *Patients at risk of cardiac or cerebral ischemia in case of acute hypotension*

The initial phase of treatment requires special medical supervision.

- *Elderly*

See section 4.2.

Surgery

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

Monitoring of renal function

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

Hypersensitivity/angioedema
Angioedema 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.
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).

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.

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.

Hyperkalaemia
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers and in elderly patients (aged >70 years), in patients with uncontrolled diabetes mellitus, or those using other plasma potassium increasing active substances, or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis hyperkalemia can occur.

Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

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

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

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

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

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.

Linked to indapamide

Special warnings
When liver function is impaired, thiazide-related diuretics may cause hepatic encephalopathy, particularly in case of electrolyte imbalance. Administration of the diuretic must be stopped immediately if this occurs.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of indapamide is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Water and electrolyte balance
- *Plasma sodium*

This must be measured before starting treatment, then at regular intervals subsequently. Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients (see sections 4.8 and 4.9). Hyponatraemia with hypovolaemia may be responsible of dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.

- *Plasma potassium*

Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. The risk of onset of hypokalaemia (<3.4 mmol/l) must be prevented in certain high risk populations, *i.e.* the

elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal *torsades de pointes.*

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment. Detection of hypokalaemia requires its correction. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

- *Plasma magnesium*

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

- *Plasma calcium*

Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism. Treatment should be withdrawn before the investigation of parathyroid function.

Blood glucose

Monitoring of blood glucose is important in diabetics, in particular in the presence of hypokalaemia.

Uric acid

Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics

Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25 mg/l, *i.e*. 220 µmol/l in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.
Hypovolaemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and plasma creatinine. This transitory functional renal insufficiency is of no consequence in individuals with normal renal function but may worsen preexisting renal insufficiency.

Athletes

The attention of athletes is drawn to the fact that this drug contains indapamide which may give a positive reaction in doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated

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.

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

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).

Concomitant use not recommended

Lithium: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of ramipril combined with indapamide with lithium is not recommended, but if the combination proves necessary, careful monitoring of plasma lithium and dose adjustment are required.

Concomitant use which requires special care

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

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

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

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

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).

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

Non-steroidal anti-inflammatory drugs, including COX-2 selective inhibitors, acetylsalicylic acid: Reduction of the antihypertensive effect 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. Moreover there is also a risk of acute renal failure in dehydrated patients (decreased glomerular filtration). The combination should be administered with caution. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Medicines increasing the risk of angioedema
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). Caution should be used when starting therapy (see section 4.4).

Torsades de pointes-inducing drugs:
- class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide),
- some antipsychotics:
  - phenothiazines (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
  - benzamides (amisulpride, sulpiride, sultopride, tiapride),
  - butyrophenones (droperidol, haloperidol),
  - others: bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV.

Increased risk of ventricular arrhythmias, particularly *torsades de pointes* (hypokalaemia is a risk factor). Monitor for hypokalaemia and correct, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.
Use substances which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.

Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives: Increased risk of hypokalaemia (additive effect). Monitoring of plasma potassium and correction if required. Must be particularly borne in mind in case of concomitant digitalis treatment. Non-stimulant laxatives should be used.

Baclofen: Increased antihypertensive effect. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy.

Digitalis preparations: Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis. Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjusting the treatment.

Concomitant use which requires some care:

Potassium-sparing diuretics (amiloride, spironolactone, triamterene): Whilst rational combinations are useful in some patients, hypokalaemia (particularly in patients with renal failure or diabetes) or hyperkalaemia may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin: Increased risk of metformin induced lactic acidosis due to the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics. Do not use metformin when plasma creatinine exceeds 15 mg/l (135 µmol/l) in men and 12 mg/l (110 µmol/l) in women.

Iodinated contrast media: In the presence of dehydration caused by diuretics, increased risk of acute renal failure, in particular when large doses of iodinated contrast media are used.
Rehydration should be carried out before administration of the iodinated compound.

Imipramine-like antidepressants, neuroleptics: Antihypertensive effect and increased risk of orthostatic hypotension increased (additive effect).

Calcium (salts): Risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Ciclosporin, tacrolimus: Risk of increased plasma creatinine without any change in circulating cyclosporin levels, even in the absence of water/sodium depletion.

Corticosteroids, tetracosactide (systemic route): Decreased antihypertensive effect (water/sodium retention due to corticosteroids).

4.6 Fertility, pregnancy and lactation

Pregnancy
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. [Invented name] is contraindicated during the second and third trimesters of pregnancy.

Linked 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 trimester 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See also 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).

Linked to indapamide
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women. Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foeto-placental ischaemia and growth retardation.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of indapamide during pregnancy.

Breast-feeding
[Invented name] is contraindicated during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue [Invented name] taking account the importance of this therapy for the mother.

Linked 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.

Linked to indapamide
There is insufficient information on the excretion of indapamide/metabolites in human milk.
Hypersensitivity to sulfonamide-derived medicines and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded.
Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decrease or even suppression of milk lactation.
Indapamide should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

[Invented name] has minor or moderate influence on the ability to drive and use machines. If patients suffer from decrease in blood pressure dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

The adverse events, that have been seen with either ramipril or indapamide alone may be potential side effects with [Invented name].

Summary of safety profile
Ramipril
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.

Indapamide
The most commonly reported adverse reactions to indapamide are hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

Tabulated list of adverse reactions
Estimated frequencies of reactions are ranked according to the following convention: 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 available data).

MedDRA system organ class	Frequency	Ramipril	Indapamide
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		Thrombocytopenia, leucopenia, aplastic anaemia, haemolytic anaemia
	Not known	Bone marrow failure, pancytopenia, haemolytic anaemia	
Immune system 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	Hypokalaemia (see section 4.4)
	Uncommon	Anorexia, decreased appetite	Hyponatraemia (see section 4.4)
	Rare		Hypochloraemia, hypomagnesaemia
	Very rare		Hypercalcaemia
	Not known	Blood sodium decreased	

Psychiatric disorders	Uncommon	Depressed mood, anxiety, nervousness, restlessness, sleep disorder including somnolence	
	Rare	Confusional state	
	Not known	Disturbance in attention	
Nervous system disorders	Common	Headache, dizziness	
	Uncommon	Vertigo, paraesthesia, ageusia, dysgeusia	
	Rare	Tremor, balance disorder	Vertigo, fatigue, headache, paresthesia
	Not known	Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, burning sensation, parosmia	
Eye disorders	Uncommon	Visual disturbance including blurred vision	
	Rare	Conjunctivitis	
	Not known		Choroidal effusion
Ear and labyrinth disorders	Rare	Hearing impaired, tinnitus	
Cardiac disorders	Uncommon	Myocardial ischaemia including angina pectoris or myocardial infarction, tachycardia, arrhythmia, palpitations, oedema peripheral	
	Very rare		Arrhythmia
	Not known		Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)
Vascular disorders	Common	Hypotension, orthostatic blood pressure decreased, syncope	
	Uncommon	Flushing	
	Rare	Vascular stenosis, hypoperfusion, vasculitis	
	Very rare		Hypotension
	Not known	Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders	Common	Non-productive tickling cough, bronchitis, sinusitis, dyspnoea	
	Uncommon	Bronchospasm including asthma aggravated, nasal congestion	
Gastrointestinal disorders	Common	Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, diarrhoea, nausea, vomiting	
	Uncommon	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel	Vomiting

		angioedema, abdominal pain upper including gastritis, constipation, dry mouth	
	Rare	Glossitis	Nausea, constipation, dry mouth
	Very rare		Pancreatitis
	Not known	Aphthous stomatitis	
Hepatobiliary disorders	Uncommon	Hepatic enzymes and/or bilirubin conjugated increased	
	Rare	Jaundice cholestatic, hepatocellular damage	
	Very rare		Abnormal hepatic function
	Not known	Acute hepatic failure, cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional)	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4), hepatitis
Skin and subcutaneous tissue disorders	Common	Rash in particular maculopapular	Hypersensitivity reactions, maculopapular rashes
	Uncommon	Angioedema; very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome; pruritus, hyperhidrosis	Purpura
	Rare	Exfoliative dermatitis, urticaria, onycholysis	
	Very rare	Photosensitivity reaction (see section 4.4)	Urticaria, toxic epidermic necrolysis, Steven-Johnson syndrome
	Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, pemphigus, psoriasis aggravated, dermatitis psoriasiform, pemphigoid or lichenoid exanthema or enanthema, alopecia	Possible worsening of pre-existing acute disseminated lupus erythematosus
Musculoskeletal and connective tissue disorders	Common	Muscle spasms, myalgia	
	Uncommon	Arthralgia	
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	
	Very rare		Renal failure
Reproductive system and breast disorders	Uncommon	Transient erectile impotence, libido decreased	Erectile dysfunction
	Not known	Gynaecomastia	
General disorders and administration site conditions	Common	Chest pain, fatigue	
	Uncommon	Pyrexia	
	Rare	Asthenia	

Investigations	Not known		Electrocardiogram QT prolonged (see sections 4.4 and 4.5). Blood glucose increased (see section 4.4). Blood uric acid increased (see section 4.4). Elevated liver enzyme levels.

Description of selected adverse reactions
During phase II and III studies comparing indapamide 1.5 mg and 2.5 mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- Indapamide 1.5 mg: Plasma potassium <3.4 mmol/l was seen in 10 % of patients and <3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.
- Indapamide 2.5 mg: Plasma potassium <3.4 mmol/l was seen in 25 % of patients and <3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

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 national reporting system listed in Appendix V.

4.9 Overdose

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

Linked to indapamide
Indapamide has been found free of toxicity at up to 40 mg, *i.e.* 27 times the therapeutic dose.
Signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatraemia, hypokalaemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).

Treatment
Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal, followed by restoration of water/electrolyte balance to normal in a specialised centre.

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 and diuretics
ATC code: C09BA05

[Invented name] is a combination of ramipril, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Mechanism of action

Linked to ramipril
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.

Linked to indapamide
Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to thiazide diuretics, which acts by inhibiting the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

Pharmacodynamic effects

Linked to ramipril
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.

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.

Linked to indapamide
Phase II and III studies using monotherapy have demonstrated an antihypertensive effect lasting 24 hours. This was present at doses where the diuretic effect was of mild intensity.
The antihypertensive activity of indapamide is related to an improvement in arterial compliance and a reduction in arteriolar and total peripheral resistance.
Indapamide reduces left ventricular hypertrophy.
Thiazide and related diuretics have a plateau therapeutic effect beyond a certain dose, while adverse effects continue to increase. The dose should not be increased if treatment is ineffective.
It has also been shown, in the short-, mid- and long-term in hypertensive patients, that indapamide:
- does not interfere with lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol;
- does not interfere with carbohydrate metabolism, even in diabetic hypertensive patients.

Paediatric population
Linked to ramipril
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

The co administration of ramipril and indapamide does not change their pharmacokinetic properties by comparison to separate administration.

Absorption
Linked to ramipril
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.

Linked to indapamide
The fraction of indapamide released is rapidly and totally absorbed via the gastrointestinal digestive tract.
Eating slightly increases the rapidity of absorption but has no influence on the amount of the drug absorbed.
Peak serum level following a single dose occurs about 12 hours after ingestion, repeated administration reduces the variation in serum levels between 2 doses. Intra-individual variability exists.

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

Linked to indapamide
Binding of indapamide to plasma proteins is 79%.
The plasma elimination half-life is 14 to 24 hours (mean 18 hours).
Steady state is achieved after 7 days.
Repeated administration does not lead to accumulation.

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

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

Linked to indapamide
Elimination is essentially urinary (70% of the dose) and faecal (22%) in the form of inactive metabolites.

Special population

Linked to ramipril
Patients with renal impairment (see section 4.2)
Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with hepatic impairment (see section 4.2)
In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed, due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

Paediatric population
The pharmacokinetic profile of ramipril was studied in 30 paediatric hypertensive patients, aged 2-16 years, weighing >10 kg. After doses of 0.05 to 0.2 mg/kg, ramipril was rapidly and extensively metabolized to ramiprilat. Peak plasma concentrations of ramiprilat occurred within 2-3 hours. Ramiprilat clearance highly correlated with the log of body weight ($p<0.01$) as well as dose ($p<0.001$). Clearance and volume of distribution increased with increasing children age for each dose group. The dose of 0.05 mg /kg in children achieved exposure levels comparable to those in adults treated with ramipril 5mg. The dose of 0.2 mg/kg in children resulted in exposure levels higher than the maximum recommended dose of 10 mg per day in adults.

<u>High risk individuals</u>
Linked to indapamide
Pharmacokinetic parameters are unchanged in renal failure patients.

5.3 Preclinical safety data

Linked 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 fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight or higher.
Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.
Irreversible kidney damage has been observed in very young rats given a single dose of ramipril.

Linked to indapamide
Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

The highest doses administered orally to different animal species (40 to 8000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms of poisoning during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, *i.e*. bradypnoea and peripheral vasodilation.
Reproductive toxicity studies have not shown embryotoxicity and teratogenicity.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Microcrystalline cellulose
Mannitol
Magnesium stearate

Capsule shell:
Gelatin (bovine)
[Invented name] 5 mg/2.5 mg; 10 mg/1.25 mg; 10 mg/2.5 mg
Iron oxide red (E172)

[Invented name] 5 mg/1.25 mg; 5 mg/2.5 mg; 10 mg/1.25 mg
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

[Invented name] 5 mg/2.5 mg
1 year

[Invented name] 5 mg/1.25 mg; 10 mg/1.25 mg; 10 mg/2.5 mg
18 months

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Aluminium/OPA/Aluminium/PVC blisters in cartons of 28 and 84 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:

10. DATE OF REVISION OF THE TEXT