PRODUCT MONOGRAPH

Pr prv-RAMIPRIL

Ramipril Capsules, USP

2.5 mg, 5 mg and 10 mg

Angiotensin Converting Enzyme Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION
SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Capsules 2.5 mg 5 mg 10 mg	For a complete listing see Dosage Forms, Composition and Packaging Section.

INDICATIONS AND CLINICAL USE

prv-RAMIPRIL is indicated for:

- **Treatment of Essential Hypertension.** It may be used alone or in association with thiazide diuretics or with the Ca channel blocker felodipine.

The safety and efficacy of ramipril in renovascular hypertension have not been established and therefore, its use in this condition is not recommended.

Geriatrics (> 65 years of age)
Although clinical experience has not identified differences in response between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatrics (<18 years of age)
The safety and effectiveness of prv-RAMIPRIL in children have not been established. Therefore, prv-RAMIPRIL is not indicated in this patient population.

CONTRAINDICATIONS

Ramipril is contraindicated in:

- Patients who are hypersensitive to this drug, to any other ACE inhibitor, or to any ingredient in the formulation. For a complete listing of ingredients see Dosage Forms, Composition and Packaging section of the product monograph.
  - Patients who have a history of angioedema.
  - Pregnant women (see WARNINGS AND PRECAUTIONS, **Special Populations, Pregnant Women**).
  - Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).
  - Patients with hemodynamically relevant bilateral renal artery stenosis, or unilateral in the single kidney (see WARNINGS AND PRECAUTIONS, **Renal, Renal impairment**).
  - Patients with hypotensive states or hemodynamically unstable states.
  - Combination with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR<60 mL/min/1.73 m^2) [see WARNINGS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS)].
  - Combination with angiotensin II receptor antagonists (ARBs) in patients with diabetic nephropathy [see WARNINGS and PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS)].
  - Combination with extracorporeal treatments leading to contact of blood with negatively charged surfaces since such use may lead to anaphylactoid reactions. Such extracorporeal treatments include dialysis or hemofiltration with certain high-flux (e.g. polyacrylonitrile) membranes and low-density lipoprotein apheresis with dextran sulfate (see WARNINGS AND PRECAUTIONS, **Immune**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ramipril should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

General

Cough

A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ramipril, has been reported. Such possibility should be considered as part of the differential diagnosis of cough (see ADVERSE REACTIONS).

Driving a vehicle or performing other hazardous tasks

Some adverse effects (e.g. some symptoms of a reduction in blood pressure (BP) such as lightheadedness, dizziness, syncope) 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).

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of ACE inhibitors, such as ramipril, or of ARBs with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR<60 mL/min/1.73 m^2). Therefore, the use of prv-RAMIPRIL in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

The use of prv-RAMIPRIL in combination with an ARB is contraindicated in patients with diabetic nephropathy (see CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including ramipril, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia (see DRUG INTERACTIONS).

Cardiovascular

Aortic Stenosis

There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Hypotension

Symptomatic hypotension has occurred after administration of ramipril, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, vomiting, or in other situations in which a significant activation of the RAS is to be anticipated such as in patients with severe, and particularly malignant, hypertension, in patients with hemodynamically relevant left-ventricular outflow impediment (e.g., stenosis of the aortic valve) or in patients with hemodynamically relevant renal artery stenosis. All patients should be cautioned about this potential excessive fall in BP and advised to consult their physician.

Generally, it is recommended that dehydration, hypovolaemia or salt depletion be corrected before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed against the risk of volume overload). When these conditions have become clinically relevant, treatment with ramipril must only be started or continued if appropriate steps are taken concurrently to prevent an excessive fall in BP and deterioration of renal function.

In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in BP could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS-Clinical Trial Adverse Drug Reactions). Because of the potential fall in BP in these patients, therapy with ramipril should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ramipril is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once BP has increased after volume expansion in hypertensive patients. However, lower doses of ramipril and/or reduced concomitant diuretic therapy should be considered. In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ramipril (see ADVERSE REACTIONS-Clinical Trial Adverse Drug Reactions, Treatment Following Acute Myocardial Infarction, DOSAGE & ADMINISTRATION-Recommended Dose and Dosage Adjustment, Treatment Following Acute Myocardial Infarction).

Ramipril may lower the state of patient alertness and/or reactivity; particularly at the start of treatment (see ADVERSE REACTIONS). Patients should be cautioned to report lightheadedness, especially during the first few days of prv-RAMIPRIL therapy. If actual syncope occurs, the patients should be told to discontinue the drug and consult with their physician.

Endocrine and metabolism

Hyperkalemia and Potassium-Sparing Diuretics
Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ramipril. In most cases, these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see DRUG INTERACTIONS-Drug-Drug Interactions).

Hematologic

Neutropenia/agranulocytosis
Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ramipril cannot be excluded. Current experience with the drug shows the incidence to be rare. Hematological reactions to ACE inhibitors are more likely to occur in patients with impaired renal function and in those with concomitant collagen disease (e.g., lupus erythematosus or scleroderma) or in those treated with other drugs that may cause changes of the blood picture. Periodic monitoring of white blood cell counts should be considered (see WARNINGS AND PRECAUTIONS-Monitoring and Laboratory Tests, and ADVERSE REACTIONS-Less Common Adverse Drug reactions, Hematologic).

Patients should be told to report promptly to their physician any indication of infection (e.g. sore throat, fever) as this may be a sign of neutropenia (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Hepatic/Biliary

Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug. Elevations of liver enzymes and/or serum bilirubin have been reported with ramipril (see ADVERSE REACTIONS). Should the patient receiving ramipril experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary

investigations be carried out. Discontinuation of prv-RAMIPRIL should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. In patients with impaired liver function, response to the treatment with prv-RAMIPRIL may be either increased or reduced. In addition, in patients in whom severe liver cirrhosis with edema and/or ascites is present, the RAS may be significantly activated. Ramipril should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply (see ACTION AND CLINICAL PHARMACOLOGY–Special Populations and conditions, Hepatic Insufficiency).

Rarely, ACE inhibitors, including ramipril, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Immune

Angioedema – Head, and Neck or Extremities
Angioedema has been reported in patients with ACE inhibitors including ramipril. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, prv-RAMIPRIL should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3-0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS- Clinical Trial Adverse Drug Reactions, Essential Hypertension-Less Common Clinical Trial Adverse Drug Reactions (<1%), Body as a whole).

An increased incidence of angioedema was observed in patients taking ACE inhibitors with mTOR inhibitors (mammalian target of rapamycin inhibitors) or vildagliptin (see DRUG INTERACTIONS).

Angioedema – Intestinal
Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Angioedema, including laryngeal edema, may occur especially following the 1st dose of prv-Ramipril.

Anaphylactoid reactions during membrane exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes [e.g. polyacrylonitrile (PAN)] and treated concomitantly with an ACE inhibitor. Therefore, the use of prv-RAMIPRIL in patients dialyzed with high-flux membranes is contraindicated (see CONTRAINDICATIONS). Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid reactions during LDL apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding the ACE inhibitor therapy prior to each apheresis. Therefore, the use of prv-RAMIPRIL in patients receiving low density lipoprotein apheresis with dextran sulfate is contraindicated (see CONTRAINDICATIONS). If such treatment is required, consideration should be given to using a different type of apheresis or a different class of antihypertensive agents.

Anaphylactoid reactions during desensitization
There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (e.g. bees, wasps) venoma. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for ≥24 hours, but they have reappeared upon inadvertent rechallenge.

Nitritoid Reactions – Gold
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ramipril (see DRUG INTERACTIONS).

Peri-Operative Considerations

Surgery/anesthesia
In patients undergoing surgery or anesthesia with agents producing hypotension, ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Renal

Renal impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the RAAS, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk; therefore, discontinuation of diuretic therapy may be required.

The use of ACE inhibitors – including ramipril – or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR<60 mL/min/1.73 m^2) (see

CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs) .

Concomitant use of ACE inhibitors – including ramipril, with ARBs is contraindicated in patients with diabetic nephropathy due to risk of hyperkalemia, hypotension and renal impairment (see CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors, or aliskiren-containing drugs).

Use of ramipril should include appropriate assessment of renal function.

Ramipril should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.

Special Populations

Pregnant Women
ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, ramipril should be discontinued as soon as possible, and, if appropriate, alternative therapy should be started. Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

The use of ACE inhibitors is contraindicated during pregnancy.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have been reported following exposure in the first trimester of pregnancy.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of BP and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

It is not known if ramipril or ramiprilat can be removed from the body by hemodialysis.

Animal Data
No teratogenic effects of ramipril were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys at doses up to 2500x, 6.25x and 1250x, respectively, the maximum human dose. In rats, the highest dose (1000 mg/kg) caused reduced food intake in the dams, with consequent reduced birth weights of the pups and weight development during the lactation period. In rabbits, maternal effects were mortalities (≥100 mg/kg) and reduced body weight. In monkeys, maternal effects were mortalities (≥50 mg/kg), vomiting, and reduced weight gain.

Nursing Women
The presence of concentrations of ACE inhibitor has been reported in human milk. The use of ramipril is contraindicated during breastfeeding.

Pediatrics (<18 years of age)
The safety and effectiveness of ramipril in children have not been established. Therefore, ramipril is not indicated in this patient population.

Geriatrics (> 65 years of age)
Although clinical experience has not identified differences in response between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out. Evaluation of renal function at the beginning of treatment is recommended (see ACTION AND CLINICAL PHARMACOLOGY-Special Populations and Conditions, Geriatrics).

Monitoring and Laboratory Tests

Hematological monitoring
It is recommended that the white blood cell count be monitored to permit detection of a possible leukopenia. 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) or
– those treated with other drugs that can cause changes in the blood picture (see DRUG INTERACTIONS – Drug-Drug Interactions, Allopurinol, Immunosuppressants, Corticosteroids, Procainamide, Cytostatics and other substances that may change the blood picture).

Renal function monitoring
Use of prv-RAMIPRIL should include appropriate assessment of renal function, particularly in the initial weeks of treatment.

Particularly careful monitoring is required in patients with:
- heart failure
- renovascular disease (atherosclerotic renal artery stenosis (AS-RAS) and fibromuscular dysplasia (FMD))
- impairment of renal function
- kidney transplant
- elderly patients

Electrolyte monitoring
It is recommended that serum potassium and serum sodium be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As ramipril is an antihypertensive, the most common adverse reactions are effects secondary to its blood-pressure-lowering action.

In long-term safety studies in patients with hypertension the most commonly reported serious adverse reactions were myocardial infarction (0.3%); edema (0.2%); hypotension (0.1%); cerebrovascular accident (0.1%); and syncope (0.1%). Angioedema occurred in 0.1% patients treated with ramipril and a diuretic.

The most frequent adverse events (AEs) occurring in these trials were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); and dyspnea (1.1%). Discontinuation of therapy due to clinical AEs was required in 0.8% of patients treated with ramipril. Cough caused discontinuation of therapy in approximately 1% of patients in North American controlled clinical trials.

Post Acute Myocardial Infarction Adverse reactions (AIRE Study) considered possibly/probably related to study drug that occurred in > 1% of patients and more frequently on ramipril were: Hypotension, Cough increased, Dizziness/Vertigo, Nausea/Vomiting, Angina pectoris, Postural hypotension, Syncope, Heart failure, Severe/resistant heart failure, Myocardial infarct, Vomiting, Headache, Abnormal kidney function, Abnormal chest pain and Diarrhea. Discontinuation of therapy due to adverse reactions was required in 36.7% of post-AMI patients taking ramipril compared to 40.8% of patients receiving placebo.

The safety profile of ramipril in patients at Increased Risk of Cardiovascular Events (HOPE Study) was consistent with the post-marketing surveillance experience. Reasons for discontinuation of therapy were cough (ramipril 7.3%, placebo 1.8%), hypotension/dizziness (ramipril 1.9%, placebo 1.5%) and edema (ramipril 0.4%, placebo 0.2%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Essential Hypertension

Ramipril was evaluated for safety in >4000 hypertensive patients. Almost 500 elderly patients participated in controlled trials. Long-term safety was assessed in almost 700 patients treated for ≥1 year. There was no increase in the incidence of AEs in elderly patients given the same daily dose. The overall frequency of AEs was not related to duration of therapy or total daily dose.

Serious AEs occurring in North American placebo-controlled clinical trials with ramipril monotherapy in hypertension (n=972) were: myocardial infarction (0.3%); edema (0.2%); hypotension (0.1%); cerebrovascular accident (0.1%); syncope (0.1%). Among all North American ramipril patients (n=1,244), angioedema occurred in 0.1% patients treated with ramipril and a diuretic.

The most frequent AEs occurring in these trials with ramipril monotherapy in hypertensive patients that were treated for ≥1 year (n=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical AEs was required in 5 patients (0.8%).

In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ramipril monotherapy in North American controlled clinical trials (n=972) have required discontinuation because of cough.

Less Common Adverse Drug Reactions (<1%)

Clinical AEs occurring in <1% of patients treated with ramipril in controlled clinical trials are listed below by body system:

Body as a whole: angioedema.

Cardiovascular: angina pectoris, arrhythmia, chest pain, disturbed orthostatic regulation, exacerbation of perfusion disturbances due to vascular stenosis, flushing, myocardial infarction, palpitations, symptomatic-hypotension, syncope, tachycardia, vascular stenosis.

CNS: anxiety, amnesia, confusion, convulsions, depression, disorders of balance, hearing loss, impaired hearing, insomnia, lightheadness, nervousness, neuralgia, neuropathy, paresthesia, polyneuritis, restlessness, sleep disturbances, somnolence, tinnitus, tremor, vertigo, vision disturbances (including blurred vision).

Dermatologic: apparent hypersensitivity reactions (with manifestations of urticaria, pruritus, or rash, with or without fever), photosensitivity, purpura.

In addition, the following cutaneous or mucosal reactions may occur: erythroderma/exfoliative dermatitis, maculopapular rash, maculo-papular exanthema, onycholysis and psoriasiform exanthema.

Gastrointestinal: abdominal discomfort, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, digestive disturbances, decreased appetite, dry mouth, dyspepsia, dysphagia, gastritis, gastroenteritis, glossitis, increased levels of pancreatic enzymes, increased salivation, intestinal angioedema, nausea, pancreatitis (cases of fatal outcome have been very exceptionally reported), taste disturbance, upper abdominal pain, vomiting.

Hematologic: agranulocytosis, eosinophilia, leukopenia, thrombocytopenia (see WARNINGS AND PRECAUTIONS -Hematologic, Neutropenia/agranulocytosis section).

Hepatobiliary: increased hepatic enzymes and/or conjugated bilirubin. Rarely, ACE inhibitors, including ramipril, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death.

Renal: impaired renal function, oliguria and acute renal failure. Increases in blood urea nitrogen (BUN) and serum creatinine. Rarely, a deterioration of pre-existing proteinuria may develop (though ACE inhibitors usually reduce proteinuria) or an increase in urinary output (in connection with an improvement in cardiac performance).

Respiratory: bronchitis, bronchospasm (including aggravated asthma), increased cough, nasal congestion, sinusitis.

Other: arthralgia, arthritis, conjunctivitis, depressed mood, dyspnea, edema, epistaxis, impotence, increased sweating, loss of taste, malaise, muscle cramps, myalgia, reduced libido, transient erectile impotence, weight gain.

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, elevated erythrocyte sedimentation rate (ESR), eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may also occur.

Abnormal Hematologic and Clinical Chemistry Findings

The following abnormal hematologic and clinical chemistry findings have been reported: decreases in red blood cell count, hemoglobin or hematocrit; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; hyponatraemia; increased creatinine; increases in blood urea nitrogen (BUN); proteinuria and significant increases in serum potassium.

Post-Market Adverse Drug Reaction

Body as a whole: anaphylactoid reactions, angioedema (cases of fatal outcome have been reported), fatigue.

Cardiovascular: cerebrovascular disorders (including ischaemic stroke and transient ischaemic attack).

CNS: attention disturbances, burning sensation (mainly to skin of face or extremities), impaired psychomotor skills (impaired reactions), precipitation or intensification of Raynaud's phenomenon, smell disturbances.

Dermatologic: erythema multiforms, exacerbation of psoriasis, lichenoid exanthema, pemphigoid exanthema and enanthema, pemphigus, reversible alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis

Endocrine: Syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Gastrointestinal: aphthous stomatitis

Hematologic: bone marrow depression and hemolytic anemia (see WARNINGS AND PRECAUTIONS -Hematologic, Neutropenia/agranulocytosis section), pancytopaenia.

Hepatobiliary: acute hepatic failure, cholestatic or cytolytic jaundice, hepatitis (cases of fatal outcome have been very exceptional), in isolated cases liver damage (including acute liver failure) may occur.

Laboratory test findings: decrease in blood sodium.

Other: gynaecomastia, positive antinuclear antibodies (ANA).

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1: Established or potential drug-drug interactions

Proper name	Ref	Effect	Clinical comment
Acenocoumarol	CT	No significant change in blood pressure, thrombotest time and coagulation factors with ramipril.	In a multi-dose double-blind, placebo-controlled, pharmacodynamic interaction study with 14 patients with mild hypertension administered both ramipril and therapeutic doses of acenocoumarol, blood pressure, thrombotest time and coagulation factors were not significantly changed.
Agents Causing Renin Release	T	Increased antihypertensive effect	The antihypertensive effect of ramipril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).
Agents Increasing Serum Potassium	CT	Since ramipril decreases aldosterone production, elevation of serum potassium may occur.	Potassium sparing diuretics such as spironolactone, triamterene or amiloride, potassium supplements, or other medicinal products that may increase kalaemia should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium, since they may lead to a significant, sometimes severe, increase in serum potassium. Salt substitutes which contain potassium should also be used with caution (See also Non-steroidal anti-inflammatory agents).
Alcohol	C	Increased vasodilatation.	Alcohol may potentiate the effect of ramipril.
Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture	T		Increased likelihood of hematological reactions.
Antacids	CT	No effect	In one open-label, randomized, cross-over single dose study in 24 male subjects, it was determined that the bioavailability of ramipril and the pharmacokinetic profile of ramiprilat were not affected by concomitant administration of the antacid, magnesium and aluminum hydroxides.

Proper name	Ref	Effect	Clinical comment
Antidiabetic agents (e.g. insulin and sulfonylurea derivates)	CT	ACE inhibitors may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycaemic reactions in patients concomitantly treated with antidiabetics.	Particularly close blood glucose monitoring is, recommended in the initial phase of co-administration.
Concomitant Diuretic Therapy	CT	Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy.	The possibility of hypotensive effects after the first dose of ramipril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ramipril. If it is not possible to discontinue the diuretic, the starting dose of ramipril should be reduced and the patient should be closely observed for several hours following the initial dose and until blood pressure has stabilized (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). Regular monitoring of serum sodium is recommended in patients undergoing concurrent diuretic therapy.
Desensitization therapy		The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venoma is increased under ACE inhibition.	It is assumed that this effect may also occur in connection with other allergens.
Digoxin	CT	In one open-label study in 12 subjects administered multiple doses of both ramipril and digoxin, no changes were found in serum levels of ramipril, ramiprilat, and digoxin.	
Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE inhibitors or aliskiren-containing drugs	CT, C		Dual Blockade of the Renin-Angiotensin-System with ACE inhibitors, including ramipril, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or moderate to severe renal impairment (see CONTRAINDICATIONS). The use of ramipril in combination with an ARB is contraindicated in patients with diabetic nephropathy (see CONTRAINDICATIONS).

Proper name	Ref	Effect	Clinical comment
			Further, co-administration of ACE inhibitors, including ramipril, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS))
Gold	C	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ramipril.	
Heparin	T	Rise in serum potassium concentration is possible.	
Lithium	CT	Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium.	These drugs should be administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be further increased.
mTOR inhibitors	C	An increased incidence of angioedema was observed in patients taking ACE inhibitors and mTOR inhibitors (mammalian target of rapamycin inhibitors).	
Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid	CT	The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs (e.g. indomethacin). Concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium	Avoid if possible. If not possible, close monitoring of serum creatinine, potassium and patient's weight is recommended. Observe the patient to ensure diuretic effects are obtained. Monitor blood pressure and renal function. Increase dose if necessary or discontinue NSAID.
Other substances with antihypertensive potential (e.g. nitrates)	T	Potentiation of the antihypertensive effect is to be anticipated.	

Proper name	Ref	Effect	Clinical comment
Salt	T	Increased dietary salt intake may attenuate the antihypertensive effect of ramipril.	
Vasopressor sympathomimetics		These may reduce the antihypertensive effect of ramipril.	Particularly close blood pressure monitoring is recommended.
Vildagliptin	CT	An increased incidence of angioedema was found in patients taking ACE inhibitors and vildagliptin.	
Warfarin	CT	The co-administration of ramipril with warfarin did not alter the anticoagulant effects.	

C = Case Study; CT = Clinical Trial; T = Theoretical

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Essential Hypertension
Dosage of prv-RAMIPRIL must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure (BP) elevation and salt restriction. The dosage of other antihypertensive agents being used with prv-RAMIPRIL may need to be adjusted.

Monotherapy
The recommended initial dosage of prv-RAMIPRIL in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to BP response, generally, at intervals of ≥2 weeks. The usual dose range is 2.5-10 mg once daily. The maximum daily dose is 20 mg.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring BP just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If BP is not controlled with prv-RAMIPRIL alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of prv-RAMIPRIL.

Concomitant Diuretic Therapy
Symptomatic hypotension occasionally may occur following the initial dose of prv-RAMIPRIL and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for 2-3 days before beginning therapy with prv-RAMIPRIL to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg prv-RAMIPRIL should be used with careful medical supervision for several hours and until BP has stabilized. The dosage of prv-RAMIPRIL should subsequently be titrated (as described above) to the optimal response.

Use in renal impairment

For patients with a creatinine clearance <40 mL/min/1.73 m^2 (serum creatinine >2.5 mg/dL), the recommended initial dose is 1.25 mg prv-RAMIPRIL once daily. Dosage may be titrated upward until BP is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance <10 mL/min/1.73 m^2) the maximum total daily dose is 2.5 mg prv-RAMIPRIL.

Use in hepatic impairment
The response to the treatment with prv-RAMIPRIL may be either increased or reduced. Treatment in these patients must therefore be initiated only under close medical supervision. The maximum permitted daily dose in such cases is 2.5 mg.

OVERDOSAGE

Limited data are available regarding overdosage with ramipril in humans; only 2 cases of overdosage have been reported.

In the case of an overdose with ramipril, the most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion with normal saline.

Overdosage may cause excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, and renal failure.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Management
Primary detoxification by, for example, gastric lavage, administration of adsorbents, sodium sulfate; (if possible during the first 30 minutes). In the event of hypotension administration of α1-adrenergic agonists (e.g. norepinephrine, dopamine) or angiotensin II (angiotensinamide), which is usually available only in scattered research laboratories, must be considered in addition to volume and salt substitution.

No experience is available concerning the efficacy of forced diuresis, alteration in urine pH, haemofiltration, or dialysis in speeding up the elimination of ramipril or ramiprilat. If dialysis or haemofiltration is nevertheless considered, see also WARNINGS AND PRECAUTIONS, Immune, Anaphylactoid reactions during membrane exposure section.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ramipril is an angiotensin converting enzyme (ACE) inhibitor.

Following oral administration, ramipril is rapidly hydrolyzed to ramiprilat, its principal active metabolite.

ACE catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE activity leads to decreased levels of angiotensin II thereby resulting in decreased vasoconstriction and decreased

aldosterone secretion. The latter decrease may result in a small increase in serum potassium (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperkalemia and Potassium-Sparing Diuretics). Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal renin secretion result in increases in plasma renin activity.

ACE is identical to kininase II. Thus, ramipril may also block the degradation of the vasodepressor peptide bradykinin, which may contribute to its therapeutic effect.

Pharmacodynamics

Administration of ramipril to patients with mild to moderate essential hypertension results in a reduction of both supine and standing BP usually with little or no orthostatic change or change in heart rate. Symptomatic postural hypotension is infrequent, although this may occur in patients who are salt-and/or volume-depleted (see WARNINGS AND PRECAUTIONS).

In single dose studies, doses of 5-20 mg ramipril lowered BP within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. At recommended doses given once daily, antihypertensive effects have persisted over 24 hours.

The effectiveness of ramipril appears to be similar in the elderly (>65 years of age) and younger adult patients given the same daily doses.

In studies comparing the same daily dose of ramipril given as a single morning dose or as a twice daily dose, BP reductions at the time of morning trough blood levels were greater with the divided regimen.

While the mechanism through which ramipril lowers BP appears to result primarily from suppression of the renin-angiotensin-aldosterone system (RAAS), ramipril has an antihypertensive effect even in patients with low-renin hypertension.

The antihypertensive effect of ramipril and thiazide diuretics used concurrently is greater than that seen with either agent used alone.

Abrupt withdrawal of ramipril has not resulted in rapid increase in BP.

Pharmacokinetics

Table 2: Summary of pharmacokinetic parameters of ramipril after single doses of 2.5 mg, 5 mg and 10 mg capsules

Mean values ± SD and (range) n=12 (11 subjects in 5 mg capsule data)			
Single Dose	C_{max} [ng/mL]	t_{max} [h]	$AUC_{(0-12)}$ [ng*h/mL]
2.5 mg capsule	10.40 ± 6.93 (3.20 - 29.10)	0.69 ± 0.22 (0.50 – 1.25)	13.23 ± 9.34 (4.30 - 34.30)
5 mg capsule	21.54 ± 8.10 (11.00 - 35.20)	0.70 ± 0.31 (0.50 – 1.50)	31.71 ± 20.57 (11.60 - 70.50)
10 mg capsule	50.96 ± 22.24 (13.60 - 89.70)	0.79 ± 0.42 (0.25 – 1.50)	70.78 ± 33.65 (17.30 – 128.80)

Absorption:
Following oral administration, ramipril is rapidly absorbed with peak plasma concentrations occurring within 1 hour. The extent of absorption of ramipril is 50-60% and is not significantly altered by the presence of food in the gastrointestinal tract, although the rate of absorption is reduced.

Following a single administration of ≤5 mg of ramipril, plasma concentrations of ramipril and ramiprilat increase in a manner that is greater than proportional to dose; after a single administration of 5-20 mg of ramipril the plasma concentrations for both are dose- proportional. The non-linear pharmacokinetics observed at the lower doses of ramipril can be explained by the saturable binding of ramiprilat to ACE. At steady-state, the 24-hour AUC for ramiprilat is dose-proportional over the recommended dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg of oral ramipril was compared to 5 mg given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner. The initial rapid decline, which represents distribution of the drug, has a half-life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows 2 elimination phases. The apparent elimination phase has a half-life of 9-18 hours, and the terminal elimination phase has a prolonged half-life of > 50 hours. After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations was 13-17 hours, but was considerably prolonged at 2.5 mg (27-36 hours).

After once daily dosing, steady state plasma concentrations of ramiprilat are reached by the 4th dose. Steady-state concentrations of ramiprilat are higher than those seen after the 1st dose of ramipril especially at low doses (2.5 mg).

Distribution:
Following absorption, ramipril is rapidly hydrolyzed in the liver to its active metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat is 56%.

Metabolism:
Ramipril is almost completely metabolized to the active metabolite ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive.

Excretion:
After oral administration of ramipril, about 60% of the parent drug and its metabolites is excreted in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Special Populations and Conditions

Geriatrics:
A single dose pharmacokinetic study conducted in a limited number of elderly patients indicated that peak ramiprilat levels and the AUC for ramiprilat are higher in older patients (see WARNINGS AND PRECAUTIONS-Special Populations, Geriatrics).

Race:
The antihypertensive effect of ACE inhibitors is generally lower in black patients than in non-blacks.

Hepatic Insufficiency:
In patients with impaired liver function, plasma ramipril levels increased about 3-fold, although peak concentrations of ramiprilat in these patients were not different from those seen in patients with normal hepatic function.

Renal Insufficiency:
The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. In patients with creatinine clearance <40 mL/min/1.73 m^2, increases in C_{max} and AUC of ramipril and ramiprilat compared to normal subjects were observed following multiple dosing with 5 mg ramipril (see DOSAGE AND ADMINISTRATION-Recommended Dose and Dosage Adjustment, Use in renal impairment).

STORAGE AND STABILITY

Store prv-RAMIPRIL in original container at room temperature, (15ºC -30ºC) and not beyond the date indicated on the container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

prv-RAMIPRIL 2.5 mg, 5.0 mg and 10.0 mg contain the medicinal ingredient ramipril in quantities of 2.5 mg, 5.0 mg and 10.0 mg, respectively.

The nonmedicinal ingredients for all potencies of prv-RAMIPRIL are: pregelatinised starch and hard gelatin capsules.

Capsule Shell Composition
prv-Ramipril 2.5 mg: contains gelatin, methyl paraben, propyl paraben, carmoisine, ponceau 4R, sunset yellow and titanium dioxide.
prv-Ramipril 5 mg: contains gelatin, methyl paraben, propyl paraben, brilliant blue, carmoisine, ponceau 4R, and titanium dioxide.
prv-Ramipril 10 mg: contains gelatin, methyl paraben, propyl paraben, brilliant blue, carmoisine, erythrosine, and titanium dioxide.

prv-RAMIPRIL is available in hard gelatin capsules in the following potencies:

2.5 mg: Orange/white coloured hard gelatin capsules, size 4; with ‘2.5’ imprinted in black on body, filled with a homogenous white to off white powder.

5.0 mg: Maroon/white coloured hard gelatin capsules, size 4; with ‘5’ imprinted in black on body, filled with a homogenous white to off white powder.

10.0 mg: Blue/white coloured hard gelatin capsules, size 4; with ‘10’ imprinted in black on body, filled with a homogenous white to off white powder.

prv-RAMIPRIL 2.5 mg, 5.0 mg and 10.0 mg are packaged in white high-density polyethylene (HDPE) bottles of 100 capsules.

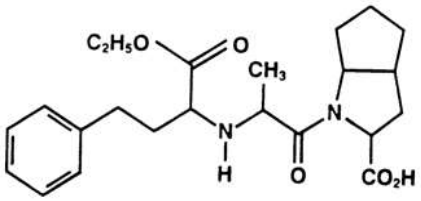
PART II: SCIENTIFIC INFORMATION
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ramipril

Chemical name: Chemical name: 2-[N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S,3S,5S)-2- azabicyclo-[3.3.0]octane-3-carboxylic acid

Structural formula:



Molecular formula: $C_{23}H_{32}N_2O_5$

Molecular mass: 416.52 g/mol

Physicochemical properties: A white to off-white crystalline powder with a melting point of 105°C to 112°C. Slightly soluble in water, and freely soluble in ethanol and methanol.

CLINICAL TRIALS

A randomized, double blinded, balanced, two treatment, two period, two sequence, single dose, two way crossover, bioequivalence study of prv-Ramipril 5.0 mg capsules of Pharmapar Inc., with Altace® (Ramipril) 5.0 mg Capsules of Sanofi-Aventis Canada Inc., was conducted on a total of 29 healthy human adult male subjects, under fasting conditions.

Ramipril (one x 5 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	prv-RAMIPRIL*	Altace†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.hr/mL)	49.015 52.909 (40.28)	51.813 57.087 (45.57)	94.38	86.78 – 102.65
AUC_∞ (ng.hr/mL)	49.937 53.876 (40.03)	53.193 58.461 (44.71)	93.68	86.04 - 102.00
C_{max} (ng/mL)	36.892 38.795 (28.92)	34.521 36.736 (35.84)	106.74	97.70 - 116.61
T_{max}@ (hr)	0.500 (0.250 – 2.000)	0.750 (0.500 – 2.500)		
$T_{½}$§ (hr)	2.132 (27.47)	3.124 (157.10)		

* prv-RAMIPRIL, by Pharmapar Inc., Canada

† Altace manufactured by Sanofi-Aventis Canada Inc. (Samples purchased in Canada)

@ Expressed as median (range) only.

§ Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Table 3: Mechanism of Action

Study	Species	#/group	Route	Dose	Results
Inhibition of Angiotensin I-induced pressor response after oral ramipril	Rat Dog	n=6 n=3	oral oral	0.1 0.3 1.0 mg/kg	A dose-dependent inhibition was observed, lasting > 6 hours
Effect of pre-treatment with ramipril on BP changes induced by i.v. Angiotensin I, Angiotensin II, and sympathomimetics	Rat	n=5 or n=6	oral	1.0 mg/kg	Effects of Ang. I and indirect-acting sympathomimetics are inhibited, while the effects of Ang. II and direct-acting sympathomimetics are unaffected by ramipril
Effect of ramipril on Na-depleted (furosemide treated) dogs	Dog	n=6	oral	10 mg/kg	Ramipril-induced increase in plasma renin activity is enhanced by furosemide; Ramipril has no influence on heart rate
In vitro inhibition of ACE by ramipril	Rabbit lung		*in vitro*		IC_{50}= 26±8 nmol/L
Effect of ramipril and captopril on renal blood flow, renal vasculature resistance, and BP	Rat	n=5	i.a.	0.1 mg/kg	Ramipril caused a greater increase in renal blood flow and decrease in renal vasculature resistance than a 10-fold higher dose of captopril; this without the decrease in systemic BP observed with captopril

Table 4: Effects on Blood Pressure

Hypertensive Model	Species	#/group	Route	Dose	Duration	Result
Spontaneously hypertensive rats	Rat	n=5	oral	1 mg/kg 0.01, 0.1, 1, 10 mg/kg/day	acute 5 weeks	Significant decreases in BP (all doses); which persisted for: 2 weeks (chronic) 72 hrs. (acute)
Kidney perinephretic hypertension (no increase in plasma renin activity)	Dog	n=5	oral	10 mg/kg 1 mg/kg/day	acute 5 days	Significant decrease of systemic BP
2 kidney, 1 clip hypertension	Rat	n=8	oral	1, 10 mg/kg	acute	BP was normalized
Release of an occluded renal pedicle	Rat	n=6	oral	0.1 mg/kg	acute	Hypertension was completely prevented

Table 5: Pharmacokinetics and Bioavailability

Study Parameter (after oral ramipril)	Results		
	Rat (2 mg/kg)	Dog (2 mg/kg)	Human (10 mg)
GI absorption of ^{14}C-ramipril	56%	43%	56%
Maximal blood levels ofradioactivity	0.5 h	0.5-1 h	0.3 h
Plasma t½ of radioactivity	0.6 h	1.0 and 3.8 h (biphasic)	0.5 and 2.9 h (biphasic)
Distribution of radioactivity	High concentration in liver, kidney and particularly lungs. Total fetus : 0.05% Breast milk: 0.25%	-	-
Serum protein binding (concentration range of 0.01-10 µg/mL)	ramipril:- ramiprilat: 41%	ramipril: 72% ramiprilat: 47%	ramipril: 73% ramiprilat: 56%
Metabolism	metabolized to ramiprilat	metabolized to ramiprilat and inactive diketopiperazines	
Excretion of radioactivity	urine: 26% feces: 71% $t_{½}$ (both): 1.6-4.8 h and 23-42 h	urine: 15% $t_{½}$: 9.3 h feces: 79% $t_{½}$: 8 h	urine: 56% $t_{½}$: 7.2 and 127 h feces: 40% $t_{½}$: 11 and 110 h

TOXICOLOGY

Acute Toxicity:

Below are summarized species-specific LD_{50} values for both oral and intravenous (iv) administrations of ramipril.

Table 6 - Acute Toxicity

Routes	Species	Sex	LD_{50}
Oral	Mouse	Male	10,933 mg/kg
		Female	10,048 mg/kg
	Rat	Male	> 10,000 mg/kg
		Female	> 10,000 mg/kg
	Dog	Male	> 1,000 mg/kg
Intravenous	Mouse	Male	1,194 mg/kg
		Female	1,158 mg/kg
	Rat	Male	688 mg/kg
		Female	609 mg/kg

The symptoms observed in mice were decreased spontaneous activity, crouching, hypothermia, dyspnea, and clonic convulsions; deaths occurred within 30 minutes after iv and 24 hours after oral administration. In survivors, the symptoms disappeared by 1-5 days after administration; necropsies revealed no abnormality in any of the surviving animals. In rats, reduced spontaneous activity was noted (oral administration), while after iv administration similar signs occurred as in mice; the sign of lethal toxicity was clonic convulsions (iv administration).

Table 7 - Chronic Toxicity

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
Mouse	28 days 90 days	2M, 2F 3M, 3F	Oral	1000	Reduced erythrocytes, hemoglobin, hematocrit, increased reticulocytes. Hyperplasia of juxtaglomerular apparatus.
Rat	30 days	10-15M, 10-15F	Oral	2.5, 80, 2500	At all doses: decrease in body weight, reduced liver weight, increased kidney weight. At ≥80 mg/kg/d: Reduced heart weight. At 2500 mg/kg/d: Reduced erythrocytes, hematocrit and bilirubin, increased BUN.
Rat	3 months	10-15M, 10-15F	Oral	2.5, 80, 500	At all doses: Reduced chloride and glutaminic-oxalacetic transaminase (GOT), increased phosphorus and blood urea nitrogen (BUN). At 80 mg/kg/d: Reduced heart, liver, prostate weights, increased kidney weight. Atrophic segments of renal tubules. Increased serum creatinine. At 500 mg/kg/d: Reduced body and heart weights, increased kidney and adrenal weights. Reduced erythrocytes, hemoglobin, hematocrit, increased bilirubin. Increased number of atrophic renal tubular segments. Moderate gastric mucosa necroses.
Rat	3 months	10M, 10F	Oral	500, 1/3 Ringer solution for drinking	Increased number of tubular atrophies.
Rat	6 months	10-20M, 10-20F	Oral	0.1, 0.25, 3.2, 40, 500	At all doses: Serum bilirubin increased, reduced heart weight. At ≥40 mg/kg/d: Increased kidney weight. Reduced erythrocytes, haemoglobin, hematocrit, increased BUN. Distal tubular atrophies, fibromuscular pad formations in gastric mucosa/ muscularis not proliferative in nature.
Rat	6 months	20M, 20F	Oral	3.2, 40, 500, 1/3 Ringer solution for drinking	All doses: Fibromuscular or solitary pad formation in gastric fundus mucosa/ muscularis.
Rat	18 months	20-25M, 20-25F	Oral	0.25, 3.2, 40, 500	At ≥3.2 mg/kg/d: Fibromuscular pads in gastric fundus mucosa, focal atrophies in renal cortex, partly with cysts. At ≥40 mg/kg/d: Anemia, increased BUN and serum creatinine, urinary epithelial cells. Reduced heart weight and increased kidney and adrenal weight.
Dog	30 days	2M, 2F	Oral	3.2, 32	No pathological findings.
Dog	3 months	3-4M, 3-4F	Oral	3.2, 32, 320	At 320 mg/kg/d: Anemia, increased BUN and serum creatinine, impaired erythropoiesis. Juxtaglomerular hyperplasia.

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
Dog	6 months	6M, 6F	Oral	3.2, 32, 320	At 32 mg/kg/d: Anemia, juxtaglomerular hyperplasia. At 320 mg/kg/d: Reduced body weight. Increased BUN and serum creatinine. Distal tubular atrophies with round cell infiltrations. Anemia, juxtaglomerular hyperplasia.
Dog	12 months	6M, 6F	Oral	2.5, 25, 250	At all doses: Reduced body weight. At ≥25 mg/kg/d: Anemia and leukopenia, impaired erythropoiesis, increased hemosiderin deposition in liver and spleen, juxtaglomerular hyperplasia. At 250 mg/kg/d: Increased BUN and serum creatinine.
Monkey	6 months	4-5M, 4-5F	Oral	0.5, 16, 500	At ≥16 mg/kg/d: Increased BUN, juxtaglomerular hyperplasia. Reduced body weight. At 500 mg/kg/d: Diarrhea, anemia, increased serum creatinine, some urinary casts, leukocytes and epithelial cells.
Monkey	6 months	5M 5F	Oral	2, 8	No pathological findings.

Table 8 - Reproduction and Teratology

Species	No. of animals per	Dose (mg/kg/day)	Duration of dosing	Results
Rat (Wistar)	32M, 32F	5, 50, 500	M 60 days before mating F14 days before mating to end of lactation	At ≥50 mg/kg/d: Parents renal pelvis enlargement, off-spring light brown discoloration of kidney tissue and dilatation of renal pelvis. At 500 mg/kg/d: Parents yellow-white coloring and induration of renal marrow. Fertility normal.
Rat (Wistar)	20F	10, 100, 1000	Days 7-17of gestation	At 1000 mg/kg/d: Reduced food consumption of mothers, reduced body weight gains of young. One young circular non-ossified area in supraoccipital bone, 1 young distortion of right scapula. No teratogenic effects.
Rat (Wistar)	20-30F	0.32, 1.25, 5, 10, 100, 1000	Day 17 of gestation to day 21 of lactation	At ≥100 mg/kg/d: Decreased gestation body weight of young, enlarged to day 21 renal pelvis up to hydronephrosis with light brown coloring of renal cortex and marrow.
Rat (Sprague-Dawley)	20F	100	Day 17 of gestation to day 21 of lactation	Young: Enlarged renal pelvis and light brown coloration of kidney tissue.
Rabbit (Himalayan)	15F	0.4, 1, 2.5	Day 6 today 18 of gestation	At 0.4 mg/kg/d: 1 abortion, 1 foetus with diaphragm hernia. At 1 mg/kg/d: 1 abortion, 1 premature delivery, 2 animals died, no animals gained weight. One dead foetus with possible hydrocephalus. At 2.5 mg/kg/d: 2 animals died, no animals gained weight, 1 foetus with diaphragm hernia, 1 with first cervical aplasia and aplasia of 1 thorax vertebra and 1 rib pair.
Monkey (Cynomolgus)	4-13F	5, 50, 500	Days 20-25 of gestation	At all doses: No sign of terato-genesis. At 5 mg/kg/d: 2 abortions, 7 diarrhea, 2 vomiting, 10 weight loss. At 50 mg/kg/d: 1 animal died, 3 abortions, 7 diarrhea, 2 vomiting, 10 weight loss. At 500 mg/kg/d: 3 animals died, 1 abortion, 4 weight loss, 4 vomiting, 4 diarrhea.

Mutagenicity:
Ramipril was not mutagenic in the Ames microbial mutagen test, the HGPRT test in V79 cells, the micronucleus test in mice and the UDS test in human A549 cells.

Carcinogenicity:
There was no evidence of a carcinogenic effect when ramipril was administered for 104 weeks to NMRI mice at doses ≤1000 mg/kg/day and to Wistar rats at doses ≤500 mg/kg/day.

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Date: Oct 20, 2015 Control No: 185056.

PART III: CONSUMER INFORMATION

Pr prv-RAMIPRIL
Ramipril Capsules, USP
2.5 mg, 5 mg and 10 mg

Read this carefully before you start taking prv-RAMIPRIL and each time you get a refill. This leaflet is a summary and will not tell you everything about prv-RAMIPRIL. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about prv-RAMIPRIL.

ABOUT THIS MEDICATION

What the medication is used for:

High Blood Pressure (Hypertension)
prv-RAMIPRIL lowers high blood pressure. It can be used alone or together with a diuretic ("water pill").

Managing your lifestyle

Keeping your blood pressure controlled

It takes more than just medication to reduce blood pressure. Discuss the risk factors, and how they apply to your lifestyle, with your doctor. You may have to modify some of your daily habits to keep your blood pressure down.

Exercise regularly. It will help to keep your weight down, make you feel more energetic and is a good way to deal with stress. If you are not exercising regularly, be sure to discuss a fitness plan with your doctor.

Remember, hypertension is a long-term disease without symptoms. Just because you feel fine does not mean you can stop taking your medication. If you stop, serious complications of the disease may occur. Therefore, you should continue to take prv-RAMIPRIL regularly, as prescribed by your doctor.

The "lifestyle" part of your treatment is as important as your medication. By working as a team with your doctor, you can help reduce the risk of complications to maintain the style of life you are accustomed to.

- **Alcohol:** Avoid alcoholic beverages until you have discussed their use with your doctor. Alcohol consumption may alter your blood pressure and/or increase the possibility of dizziness or fainting.
- **Diet:** Generally, avoid fatty foods and food that is high in salt or cholesterol.
- **Smoking:** Avoid it completely.

What it does:

prv-RAMIPRIL is an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in **'-PRIL'.**

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking prv-RAMIPRIL regularly even if you feel fine.

When it should not be used:

Do not take prv-RAMIPRIL if you:
- Are allergic to ramipril or to any non-medicinal ingredient in the formulation.
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ACE inhibitor or without a known cause. Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors, such as surgery, flu, or dental procedures.
- Are pregnant or intend to become pregnant. Taking prv-RAMIPRIL during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. Ramipril passes into breast milk.
- Have narrowing of the arteries to one or both kidneys (renal artery stenosis).
- Have hypotension (low blood pressure).
- Are on dialysis or LDL apheresis (a treatment to remove LDL cholesterol from the blood).
- Have diabetes or kidney disease and are already taking:
  - a blood pressure-lowering medicine that contains aliskiren (such as Rasilez®)
  - an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN".

What the medicinal ingredient is:
ramipril

What the nonmedicinal ingredients are:

prv-RAMIPRIL 2.5 mg: contains gelatin, methyl paraben, propyl paraben, carmoisine, ponceau 4R, sunset yellow and titanium dioxide.
prv-RAMIPRIL 5 mg: contains gelatin, methyl paraben, propyl paraben, brilliant blue, carmoisine, ponceau 4R, and titanium dioxide.

prv-RAMIPRIL 10 mg: contains gelatin, methyl paraben, propyl paraben, brilliant blue, carmoisine, erythrosine, and titanium dioxide.

prv-RAMIPRIL is available in hard gelatin capsules in the following potencies:

2.5 mg: Orange/white coloured hard gelatin capsules, size 4; with '2.5' imprinted in black on body, filled with a homogenous white to off white powder.

5.0 mg: Maroon/white coloured hard gelatin capsules, size 4; with '5' imprinted in black on body, filled with a homogenous white to off white powder.

10.0 mg: Blue/white coloured hard gelatin capsules, size 4; with '10' imprinted in black on body, filled with a homogenous white to off white powder.

What dosage forms it comes in:
Capsules 2.5 mg, 5.0 mg and 10.0 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions – Pregnancy

prv-RAMIPRIL should not be used during pregnancy. If you discover that you are pregnant while taking prv-RAMIPRIL, stop the medication and please contact your doctor, nurse, or pharmacist as soon as possible.

BEFORE you use prv-RAMIPRIL talk to your doctor, nurse, or pharmacist if you:

- Are allergic to any drug used to lower blood pressure.
- Have recently received or are planning to get allergy shots for bee or wasp stings.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Are on dialysis or LDL apheresis (a treatment to remove LDL cholesterol from the blood).
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill") or other medicinal products that may increase potassium.. Use of prv-RAMIPRIL with these medicines is not recommended.
- Are on a low-salt diet.
- Are receiving gold (sodium aurothiomalate) injections.
- Are less than 18 years old.
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with prv-RAMIPRIL is not recommended.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN". The combination with prv-RAMIPRIL is not recommended.

You may become sensitive to the sun while taking prv-RAMIPRIL. Exposure to sunlight should be minimized until you know how you respond.

If you are going to have surgery and will be given an anesthetic, be sure to tell your doctor or dentist that you are taking prv-RAMIPRIL.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to prv-RAMIPRIL. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

Raynaud's phenomenon is a condition resulting from poor circulation in the extremities (i.e., fingers and toes). It may begin or get worse.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with prv-RAMIPRIL:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, a potassium-sparing diuretic (a specific kind of "water pill") or other medicinal products that may increase potassium. Use of prv-RAMIPRIL with these medicines is not recommended.
- Alcohol
- Allopurinol used to treat gout.
- Antidiabetic drugs, including insulin and oral medicines, in particular vildagliptin.
- Lithium used to treat bipolar disease.
- Gold for the treatment of rheumatoid arthritis.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), or angiotensin receptor blockers (ARBs).
- Nitrates used to treat angina (chest pain)
- Acetylsalicylic acid (aspirin)
- Heparin used to prevent and treat blood clots.
- Immunosuppressants used to lower the body's ability to reject a transplanted organ.
- Corticosteroids used to treat joint pain and swelling or for other conditions.
- Procainamide used to treat irregular heartbeat
- Cytostatic-medicines used to treat certain types of cancer

- mTOR inhibitors (e.g. temsirolimus) used to lower the body's ability to reject a transplant or to treat certain types of cancer.

PROPER USE OF THIS MEDICATION

Take prv-RAMIPRIL exactly as prescribed. It is recommended to take your dose at about the same time every day. Capsules should be swallowed whole. DO NOT open, divide, crush or chew the capsules.

Usual adult dose:

High Blood Pressure: The recommended initial dosage of prv-RAMIPRIL is 2.5 mg once daily. Your doctor will determine the appropriate dosage.

For patients taking diuretics ("water pills") or with impaired kidney function: The recommended initial dosage of prv-RAMIPRIL is 1.25 mg daily.

Overdose:

If you think you have taken too much prv-RAMIPRIL contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Dizziness, difficulty in maintaining your balance while standing
- drowsiness, fatigue, weakness
- cough, nasal or sinus congestion, swollen lymph nodes, bronchitis, aggravated asthma
- rash, itching, flushing, inflammation of the eye (pink eye), skin inflammation or red skin, burning sensation, inflammation of the mouth or tongue.
- headache
- abdominal pain
- sad mood, difficulty with sleep, restlessness, attention disturbances.
- loss of hair
- taste modifications or loss of taste, vision or hearing modifications.
- Impotence/reduced libido, breast enlargement in males

If any of these affects you severely, tell your doctor, nurse or pharmacist.

prv-RAMIPRIL can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/Effect		Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.	√		
	Increased levels of potassium in the blood: irregular heartbeat, muscle weakness and generally feeling unwell		√	
Uncommon	**Allergic Reaction:** rash, Hives, swelling of the face, arms and legs, lips, tongue or throat, difficulty swallowing or breathing			√
	Kidney Disorder: change In frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
	Electrolyte Imbalance:weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
Rare	**Decreased Platelets:** bruising, bleeding, fatigue and weakness		√	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
	Heart Attack: chest pain and/or discomfort, pain in the jaw, shoulders, arm and/or back, shortness of breath, sweating, lightheadedness, nausea			√
	Cerebrovascular accident/Stroke: weakness, trouble speaking, trouble seeing, headache, dizziness			√
	Intestinal Angioedema: abdominal pain (with or without nausea or vomiting)			√

This is not a complete list of side effects. For any unexpected effects while taking prv-RAMIPRIL, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store in original container at room temperature (15-30ºC). Protect from light and moisture, and not beyond the date indicated on the container.

Keep out of reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to:
Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9
Postage paid labels and the Consumer Side Effect Reporting Form are available at
NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This information for the consumer was prepared by Pharmapar Inc.

This document plus the full product monograph, prepared for health professionals can be found by contacting:

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