

PRODUCT MONOGRAPH

^{Pr}**RAMIPRIL CAPSULES**

Ramipril Capsules, Manufacturer's Standard

Capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg

Angiotensin Converting Enzyme Inhibitor

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Pr **RAMIPRIL CAPSULES**

Ramipril Capsules, Manufacturer's Standard

Capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Capsules 1.25 mg 2.5 mg 5.0 mg 10.0 mg	Black iron oxide, gelatin, potassium hydroxide, pregelatinized starch, propylene glycol, shellac, sodium lauryl sulfate, and titanium dioxide. In addition, RAMIPRIL CAPSULES 1.25 mg contains: iron oxide yellow RAMIPRIL CAPSULES 2.5 mg contains: D&C Yellow 10 and FD&C Red 40 RAMIPRIL CAPSULES 5 mg contains: FD&C Blue 1 and FD&C Red 40 RAMIPRIL CAPSULES 10 mg contains: D&C Yellow 10, FD&C Blue 2 and FD&C Red 3.

INDICATIONS AND CLINICAL USE

RAMIPRIL CAPSULES (ramipril) is indicated for:

- **Essential Hypertension**

RAMIPRIL CAPSULES is indicated in the treatment of essential hypertension. It may be used alone or in association with thiazide diuretics.

RAMIPRIL CAPSULES can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

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

The safety and efficacy of concurrent use of RAMIPRIL CAPSULES with antihypertensive agents other than thiazide diuretics or calcium channel blocker felodipine have not been established.

General

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

The safety and effectiveness of RAMIPRIL CAPSULES in children have not been established; therefore use in this age group is not recommended.

CONTRAINDICATIONS

RAMIPRIL CAPSULES 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.
- In patients who have a history of angioedema.
- During pregnancy
- In breast feeding-women
- In patients with haemodynamically relevant bilateral renal artery stenosis, or unilateral in the single kidney
- In patients with hypotensive states or hemodynamically unstable states

Concomitant use of ACE inhibitors and extracorporeal treatments leading to contact of blood with negatively charged surfaces must be avoided since such use may lead to anaphylactoid reactions (see WARNINGS AND PRECAUTIONS, Immune section). Such extracorporeal treatments include dialysis or haemofiltration with certain high-flux (e.g. polyacrylonitril) membranes and low-density lipoprotein apheresis with dextran sulfate.

Concomitant use of angiotensin converting enzyme (ACE) inhibitors – including ramipril with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment ($GFR < 60 \text{ ml/min/1.73m}^2$) is contraindicated (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) with ACE inhibitors, or ARBs in combination with aliskiren-containing drugs).

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 CAPSULES should be discontinued as soon as possible.

General

Cough

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

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as ramipril, or of angiotensin receptor antagonists (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 ($GFR < 60 \text{ ml/min/1.73m}^2$). Therefore, the use of ramipril in combination with aliskiren-containing drugs is contraindicated in these patients (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.

Patient alertness

RAMIPRIL CAPSULES may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

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 renin-angiotensin system is to be anticipated such as in patients with severe, and particularly with malignant hypertension, in patients with haemodynamically relevant left-ventricular outflow impediment (e.g., stenosis of the aortic valve) or in patients with haemodynamically relevant renal artery stenosis.

In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS-Clinical Trial Adverse Drug Reactions). Because of the potential fall in blood pressure in these patients, therapy with RAMIPRIL CAPSULES 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 CAPSULES 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.

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 CAPSULES must only be started or continued if appropriate steps are taken concurrently to prevent an excessive fall in blood pressure and deterioration of renal function.

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 the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of RAMIPRIL CAPSULES and/or reduced concomitant diuretic therapy should be considered.

Endocrine and metabolism

Hyperkalemia and Potassium-Sparing Diuretics

Elevated serum potassium (greater than 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. Periodic monitoring of white blood cell counts should be considered especially in patients with collagen vascular disease and/or renal disease (see WARNINGS AND PRECAUTIONS-Monitoring and Laboratory Tests, and ADVERSE REACTIONS-Less Common Adverse Drug reactions, Hematologic).

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 CAPSULES 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 RAMIPRIL CAPSULES 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 RAMIPRIL CAPSULES may be either increased or reduced. In addition, in patients in whom severe liver cirrhosis with oedema and/or ascites is present, the renin-angiotensin system may be significantly activated. RAMIPRIL CAPSULES 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, RAMIPRIL CAPSULES 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 to 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).

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 first dose of RAMIPRIL CAPSULES.

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. 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. In these patients 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.

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 at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Peri-Operative Considerations

Surgery/anesthesia

In patients undergoing surgery or anesthesia with agents producing hypotension, RAMIPRIL CAPSULES 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, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, 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/1.73m²). (See CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, or ACE inhibitors, in combination with aliskiren-containing drugs).

Use of RAMIPRIL CAPSULES should include appropriate assessment of renal function.

RAMIPRIL CAPSULES 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 CAPSULES should be discontinued as soon as possible.

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.

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

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 blood pressure 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. The doses used were: 10, 100, or 1000 mg/kg in rats (2500 times maximum human dose), 0.4, 1.0, or 2.5 mg/kg in rabbits (6.25 times maximum human dose), and 5, 50, or 500 mg/kg in cynomolgus monkeys (1250 times maximum human dose). In rats, the highest dose 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 (high and middle dose) and reduced body weight. In monkeys, maternal effects were mortalities (high and middle dose), vomiting, and reduced weight gain.

Nursing Women

The presence of concentrations of ACE inhibitor have been reported in human milk. The use of RAMIPRIL CAPSULES is contraindicated during breast-feeding.

Pediatrics

The safety and effectiveness of RAMIPRIL CAPSULES in children have not been established; therefore use in this age group 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. 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 RAMIPRIL CAPSULES should include appropriate assessment of renal function, particularly in the initial weeks of treatment with an ACE inhibitor. Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.

Particularly careful monitoring is required in patients with:

- heart failure
- renovascular disease, including patients with haemodynamically relevant unilateral renal artery stenosis. In the latter patient group, even a small increase in serum creatinine may be indicative of unilateral loss of renal function.
- impairment of renal function
- kidney transplant
- elderly or geriatric 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.

Driving a vehicle or performing other hazardous tasks

Some adverse effects (e.g. some symptoms of a reduction in blood pressure 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).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

The long-term safety of ramipril, as monotherapy was assessed in patients with hypertension. The most commonly reported serious adverse reactions were hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Angioedema occurred in 0.1% patients treated with ramipril and a diuretic.

The most frequent adverse events 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%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 0.8% of patients treated with ramipril. Approximately 1% of patients in North American controlled clinical trials have required discontinuation because of cough.

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

Serious adverse events occurring in North American placebo-controlled clinical trials with ramipril monotherapy in hypertension (n=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); 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 adverse events occurring in these trials with ramipril monotherapy in hypertensive patients that were treated for at least one 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 adverse events 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 adverse events occurring in less than 1% of patients treated with ramipril in controlled clinical trials are listed below by body system:

Body as a whole: angioedema.

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

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

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: maculopapular rash, maculopapular exanthema, psoriasiform exanthema, erythroderma/exfoliative dermatitis, and onycholysis.

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

Hematologic: agranulocytosis, leukopenia, eosinophilia, 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: increased cough, nasal congestion, sinusitis, bronchitis, and bronchospasm (including aggravated asthma).

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

A symptom complex has been reported which may include fever, vasculitis, myalgia,

arthralgia/arthritis, elevated ESR, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may also occur.

Abnormal Hematologic and Clinical Chemistry Findings

Increased creatinine; increases in blood urea nitrogen (BUN); decreases in red blood cell count, hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; 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: burning sensation (mainly to skin of face or extremities), smell disturbances, precipitation or intensification of Raynaud's phenomenon, impaired psychomotor skills (impaired reactions), attention disturbances.

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

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

Gastrointestinal: aphthous stomatitis

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

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 ANA.

DRUG INTERACTIONS

Drug-Drug Interactions

Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE inhibitors, or ARBs in combination with aliskiren-containing drugs:

Dual Blockade of the Renin-Angiotensin-System with ACE inhibitors, or ARBs in combination with aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and 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).

Concomitant Diuretic Therapy: 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 CAPSULES can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with RAMIPRIL CAPSULES. If it is not possible to discontinue the diuretic, the starting dose of RAMIPRIL CAPSULES 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.

Other substances with antihypertensive potential (e.g. nitrates): potentiation of the antihypertensive effect is to be anticipated.

Vasopressor sympathomimetics: These may reduce the antihypertensive effect of RAMIPRIL CAPSULES. Particularly close blood pressure monitoring is recommended.

Agents Increasing Serum Potassium: Since RAMIPRIL CAPSULES decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution (See also Non-steroidal anti-inflammatory agents).

Agents Causing Renin Release: The antihypertensive effect of RAMIPRIL CAPSULES is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Lithium: 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.

Antacids: 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.

Digoxin: 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.

Warfarin: The co-administration of ramipril with warfarin did not alter the anticoagulant effects.

Acenocoumarol: 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.

Non-steroidal anti-inflammatory agents and acetylsalicylic acid: The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of non-steroidal anti-inflammatory agents (e.g. indomethacin). Concomitant treatment of ACE inhibitors and Non-Steroidal Anti-Inflammatory drugs may lead to an increased risk of worsening of renal function and an increase in serum potassium (see also Agents Increasing Serum Potassium).

Heparin: rise in serum potassium concentration possible.

Antidiabetic agents (e.g. insulin and sulfonylurea derivatives): 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, therefore, recommended in the initial phase of co-administration.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture: increased likelihood of hematological reactions.

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.

Alcohol: increased vasodilatation. Alcohol may potentiate the effect of ramipril.

Salt: increased dietary salt intake may attenuate the antihypertensive effect of ramipril.

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.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Essential Hypertension

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

Monotherapy

The recommended initial dosage of RAMIPRIL CAPSULES in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure 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 blood pressure is not controlled with RAMIPRIL CAPSULES alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of RAMIPRIL CAPSULES.

Concomitant Diuretic Therapy

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

Use in renal impairment

For patients with a creatinine clearance below 40ml/min/1.73m² (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg RAMIPRIL CAPSULES once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10ml/min/1.73m²) the maximum total daily dose of 2.5 mg RAMIPRIL CAPSULES should not be exceeded.

Use in hepatic impairment

The response to the treatment with RAMIPRIL CAPSULES 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 of ramipril in humans. Two 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 immediately.

Management

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

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

α 1-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 CAPSULES is an angiotensin converting enzyme (ACE) inhibitor, which is used in the treatment of essential hypertension.

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

Angiotensin-converting enzyme 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 blood pressure 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 of ramipril lowered blood pressure 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 (over 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, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

While the mechanism through which RAMIPRIL CAPSULES lowers blood pressure appears to result primarily from suppression of the renin-angiotensin-aldosterone system, ramipril has an antihypertensive effect even in patients with low-renin hypertension.

The antihypertensive effect of RAMIPRIL CAPSULES 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 blood pressure.

Pharmacokinetics

Table 1: 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 up to 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 mg to 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 two 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 fourth dose. Steady-state concentrations of ramiprilat are higher than those seen after the first dose of RAMIPRIL CAPSULES 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 CAPSULES, 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 angiotensin converting enzyme 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 m², 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 RAMIPRIL CAPSULES in original container at room temperature (15° C - 30° C). Protect from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RAMIPRIL CAPSULES 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg contain the medicinal ingredient ramipril in quantities of 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg respectively.

The nonmedicinal ingredients for all potencies of RAMIPRIL CAPSULES are: pregelatinized starch.

Capsule Shell Composition

RAMIPRIL CAPSULES 1.25 mg: contains gelatin, iron oxide yellow sodium lauryl sulfate and titanium dioxide.

RAMIPRIL CAPSULES 2.5 mg: contains D&C Yellow 10, FD&C Red 40, gelatin, sodium lauryl sulfate and titanium dioxide.

RAMIPRIL CAPSULES 5 mg: contains FD&C Blue 1, FD&C Red 40, gelatin, sodium lauryl sulfate and titanium dioxide.

RAMIPRIL CAPSULES 10 mg: contains D&C Yellow 10, FD&C Blue 2, FD&C Red 3, gelatin, sodium lauryl sulfate and titanium dioxide.

Capsule Imprinting Ink Composition: Black Iron Oxide, Potassium Hydroxide, Propylene Glycol, and Shellac

RAMIPRIL CAPSULES is available in hard gelatin capsules in the following potencies:

- | | |
|---------|---|
| 1.25 mg | Yellow opaque cap and white opaque body, self lock hard gelatin capsules of size '4' imprinted with 'RANBAXY' on cap and 'R-1.25' on body containing white to off-white powder. |
| 2.5 mg | Orange opaque cap and white opaque body, self lock hard gelatin capsules of size '4' imprinted with 'RANBAXY' on cap and 'R-2.5' on body containing white to off-white powder. |
| 5.0 mg | Red opaque cap and white opaque body, self lock hard gelatin capsules of size '4' imprinted with 'RANBAXY' on cap and 'R-5' on body containing white to off-white powder. |
| 10.0 mg | Blue opaque cap and white opaque body, self lock hard gelatin capsules of size '4' imprinted with 'RANBAXY' on cap and 'R-10' on body containing white to off-white powder. |

RAMIPRIL CAPSULES 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg are packaged in white opaque high-density polyethylene (HDPE) bottles of 100 and 500 capsules and blisters of 30.

PART II: SCIENTIFIC INFORMATION

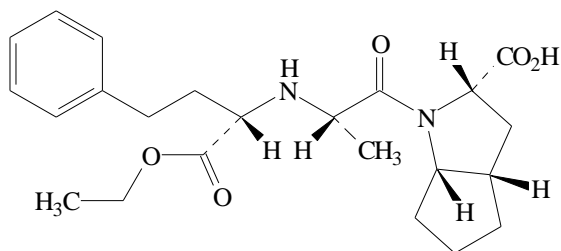
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ramipril

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: C₂₃H₃₂N₂O₅

Molecular mass: 416.5 g/mol

Physicochemical properties: A white or almost white, crystalline powder. Slightly soluble in water, and freely soluble in methanol.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single-dose, blinded, randomized, two-way crossover bioequivalence study of RAMIPRIL CAPSULES (Ranbaxy Pharmaceuticals Canada Inc.) *versus* Altace® (Hoechst Marion Roussel, currently Sanofi-Aventis Canada Inc.), each administered as a 1 x 10 mg capsule dose, was conducted on a total of 50 healthy male volunteers under fasting conditions. The table below summarizes the results:

Ramipril (1 x 10 mg capsules) From measured data Geometric Mean/ Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	% Ratio of Geometric Means#	90% Confidence Interval#
AUC _{0-T} (ng-hr/mL)	24.5628/ 26.2654 (39.8%)	24.2266/ 26.9346 (65.3%)	101.72	95.99 – 107.79
AUC ₀₋₁ (ng-hr/mL)	25.4755/ 27.2867 (39.8%)	25.1423/ 27.8912 (64.2%)	101.89	95.95 – 108.19
C _{max} (ng/mL)	40.0683/ 48.5713 (64.9%)	41.4356/ 50.8213 (84.0%)	97.59	85.33-111.60
T _{max} (h)	0.5778 (0.18183)	0.5066 (0.17873)	-	-
Kel (1/h)	0.8602 (0.38398)	0.7883 (0.32115)	-	-
T _{1/2} (h)	1.1311 (0.97617)	1.1365 (0.80563)	-	-

* RAMIPRIL CAPSULES 10 mg capsules (Ranbaxy Pharmaceuticals Canada Inc.)

† Altace® 10 mg capsules (Hoechst Marion Roussel Canada Inc., currently Sanofi-Aventis Canada Inc.) was purchased in Canada

Calculation based on least squares estimate

~ Expressed as Arithmetic Mean (CV%) only

DETAILED PHARMACOLOGY

Table 2: 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 more than 6 hours
Effect of pre-treatment with ramipril on b.p. 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		<i>in vitro</i>		IC ₅₀ = 26±8 nmol/L
Effect of ramipril and captopril on renal blood flow, renal vasculature resistance, and blood pressure	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 b.p. observed with captopril

Table 3: 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 b.p.(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 blood pressure
2 kidney, 1 clip hypertension	Rat	n=8	oral	1,10 mg/kg	acute	Blood pressure was normalized
Release of an occluded renal pedicle	Rat	n=6	oral	0.1 mg/kg	acute	Hypertension was completely prevented

Table 4: Pharmacokinetics and Bioavailability

Study Parameter (after oral ramipril)	Results		
	Rat (2 mg/kg)	Dog (2 mg/kg)	Human (10 mg)
GI absorption of 14C-ramipril	56%	43%	56%
Maximal blood levels of radioactivity	0.5 hrs	0.5-1 hrs	0.3 hrs
Plasma t _{1/2} of radioactivity	0.6 hrs	1.0 and 3.8 hrs (biphasic)	0.5 and 2.9 hrs (biphasic)
Distribution of radioactivity	High concentration in liver, kidney and particularly lungs. Total foetus : 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 _{1/2} (both): 1.6-4.8 and 23-42 h	urine: 15% t _{1/2} : 9.3 h feces: 79% t _{1/2} : 8 h	urine: 56% t _{1/2} : 7.2 and 127 h feces: 40% t _{1/2} : 11 and 110 h

TOXICOLOGY

Acute Toxicity:

Below are summarized species-specific LD₅₀ values for both oral and intravenous administrations of ramipril.

Table 5 - Acute Toxicity

Routes	Species	Sex	LD₅₀
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 intravenous and 24 hours after oral administration. In survivors, the symptoms disappeared by 1 to 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 intravenous administration similar signs occurred as in mice; the sign of lethal toxicity was clonic convulsions (intravenous administration).

Table 6 - 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 & 2500 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 GOT, increased phosphorus and BUN. At 80 mg/kg/d: Reduced heart, liver, prostate weight, increased kidney weight. Atrophic segments of renal tubules. Increased serum creatinine. At 500 mg/kg/d: Reduced body and heart weight, increased kidney and adrenal weight. 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.

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
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 and 500 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 to 500 mg/kg/d: Fibromuscular pads in gastric fundus mucosa, focal atrophies in renal cortex, partly with cysts. At 40 and 500 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.
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.

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
Dog	12 months	6M, 6F	Oral	2.5, 25, 250	At all doses: Reduced body weight. At 25 and 250 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 and 500 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 7 - Reproduction and Teratology

Species	No. of animals per group	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 and 500 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 7-17 of 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 and 1000 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 to day 18 of gestation	At 0.4 mg/kg/d: One abortion, one foetus with diaphragm hernia. At 1 mg/kg/d: One abortion, one premature delivery, two animals died, no animals gained weight. One dead foetus with possible hydrocephalus. At 2.5 mg/kg/d: Two animals died, no animals gained weight, one foetus with diaphragm hernia, one with first cervical aplasia and aplasia of one thorax vertebra and one rib pair.

Species	No. of animals per group	Dose (mg/kg/day)	Duration of dosing	Results
Monkey (Cynomolgus)	4-13F	5, 50, 500	Days 20-25 of gestation	<p>At all doses: No sign of teratogenesis.</p> <p>At 5 mg/kg/d: Two abortions, seven diarrhea, two vomiting, ten weight loss.</p> <p>At 50 mg/kg/d: One animal died, three abortions, seven diarrhea, two vomiting, ten weight loss.</p> <p>At 500 mg/kg/d: Three animals died, one abortion, four weight loss, four vomiting, four diarrhea.</p>

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 up to 1000 mg/kg/day and to Wistar rats at doses up to 500 mg/kg/day.

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PART III: CONSUMER INFORMATION

Pr RAMIPRIL CAPSULES

Ramipril Capsules, Manufacturer’s Standard

Capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg

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

ABOUT THIS MEDICATION

What the medication is used for:

High Blood Pressure (Hypertension)

RAMIPRIL CAPSULES 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 RAMIPRIL CAPSULES 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:

RAMIPRIL CAPSULES 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 RAMIPRIL CAPSULES regularly even if you feel fine.

When it should not be used:

Do not take RAMIPRIL CAPSULES 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 RAMIPRIL CAPSULES 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 already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes and/or kidney disease.

What the medicinal ingredient is:

ramipril

What the nonmedicinal ingredients are:

Non-medicinal ingredients in all capsules include: black iron oxide, gelatin, potassium hydroxide, pregelatinized starch, propylene glycol, shellac, sodium lauryl sulfate, and titanium dioxide.

In addition, RAMIPRIL CAPSULES 1.25 mg contains: iron oxide yellow

RAMIPRIL CAPSULES 2.5 mg contains: D&C Yellow 10 and FD&C Red 40

RAMIPRIL CAPSULES 5 mg contains: FD&C Blue 1 and FD&C Red 40

RAMIPRIL CAPSULES 10 mg contains: D&C Yellow 10, FD&C Blue 2 and FD&C Red 3.

What dosage forms it comes in:

Capsules 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy

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

BEFORE you use RAMIPRIL CAPSULES 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 heart failure.
- Have diabetes, liver or kidney disease.
- Are on dialysis.
- 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”). Use of RAMIPRIL CAPSULES 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 RAMIPRIL CAPSULES is not recommended.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in “-SARTAN”.

You may become sensitive to the sun while taking RAMIPRIL CAPSULES. 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 RAMIPRIL CAPSULES.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to RAMIPRIL CAPSULES. 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 RAMIPRIL CAPSULES:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of “water pill”). Use of RAMIPRIL CAPSULES with these medicines is not recommended.
- Allopurinol used to treat gout.

- Antidiabetic drugs, including insulin and oral medicines.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib.
- Other blood pressure lowering drugs, including diuretics (“water pills”). When taken in combination with RAMIPRIL CAPSULES, they may cause excessively low blood pressure.
- Nitrates
- ASA (aspirin)
- Heparin
- Immunosuppressants
- Corticosteroids
- Procainamide
- Cytostatics.
- Other substances that may change the normal results expected to be measured on a routine blood test.
- Blood pressure-lowering drugs, including diuretics (“water pills”), aliskiren-containing products (e.g. Rasilez), or angiotensin receptor blockers (ARBs).

PROPER USE OF THIS MEDICATION

Take RAMIPRIL CAPSULES exactly as prescribed. It is recommended to take your dose at about the same time everyday.

Usual adult dose:

High Blood Pressure: The recommended initial dosage of RAMIPRIL CAPSULES 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 RAMIPRIL CAPSULES is 1.25 mg daily.

Overdose:

If you think you have taken too much RAMIPRIL CAPSULES 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
- drowsiness, fatigue, weakness
- cough
- rash, itching, flushing
- headache
- abdominal pain
- sad mood

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

Other side effects may include: difficulty in maintaining your balance while standing, nasal or sinus congestion, swollen lymph nodes, bronchitis, loss of hair, impotence/reduced libido, difficulty with sleep, restlessness, inflammation of the eye (pink eye), taste modifications or loss of taste, vision or hearing modifications, attention disturbances, skin inflammation or red skin, burning sensation, inflammation of the mouth or tongue, aggravated asthma, breast enlargement in males.

RAMIPRIL CAPSULES 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	√		
	Increased levels of potassium in the blood: irregular heartbeat, muscle weakness and generally feeling unwell		√	
	Allergic Reaction: rash, hives, swelling of the face, arms and legs, lips, tongue or throat, difficulty swallowing or breathing			√
Uncommon	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		√	

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	
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			√
	Cerebro-vascular 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 RAMIPRIL CAPSULES, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store in original container at room temperature, between 15° C - 30° C. Protect from light and moisture.

Keep out of reach and sight of children.

REPORTING SUSPECTED 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, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

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 document plus the full product monograph, prepared for health professionals can be obtained by contacting Ranbaxy Pharmaceuticals Canada Inc., at: 1-866-840-1340.

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