PRODUCT MONOGRAPH

[Pr] AVA-RAMIPRIL
Ramipril

Tablets 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg

Pharmaceutical Standard: Professed

Angiotensin Converting Enzyme Inhibitor

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Ava-Ramipril

(Ramipril tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg	Not applicable For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

INDICATIONS AND CLINICAL USE

Ava-Ramipril (ramipril) is indicated for:

- **Essential Hypertension**

Ava-Ramipril is indicated in the treatment of essential hypertension. It may be used alone or in association with thiazide diuretics.

Ava-Ramipril should normally be used in patients in whom treatment with a diuretic or a beta blocker was found ineffective or has been associated with unacceptable adverse effects.

Ava-Ramipril 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 Ava-Ramipril 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 Ava-Ramipril with antihypertensive agents other than thiazide diuretics have not been established.

General
In using ramipril consideration should be given to the risk of angioedema (see **WARNINGS AND PRECAUTIONS**, **IMMUNE**, **Angioedema**).

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** and **INFORMATION FOR THE PATIENT**).

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 in children have not been established; therefore use in this age group is not recommended.

CONTRAINDICATIONS

Ramipril is contraindicated in:

- Patients who are hypersensitive to this drug, to any other ACE inhibitor, or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Patients who have a history of angioedema.
- During pregnancy
- In breast feeding women

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.

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**).

Patient Alertness
Ramipril 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, or vomiting. 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**, and **LESS COMMON CLINICAL TRIAL ADVERSE DRUG REACTIONS (<1%)**, **Cardiovascular**). Because of the potential fall in blood pressure 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 the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of ramipril and/or reduced concomitant diuretic therapy should be considered.

HEMATOLOGIC

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**).

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leucopenia 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**.)

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 preexisting 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 ramipril should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Ramipril should be used with particular caution in patients with preexisting 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.

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

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 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** and **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.

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 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
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.

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.

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 is contraindicated during breast feeding.

Pediatrics: The safety and effectiveness of ramipril 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 (see **ACTION AND CLINCAL PHARMACOLOGY, SPECIAL POPULATIONS AND CONDITIONS**, **Geriatrics**).

MONITORING AND LABORATORY TESTS

Hematological Monitoring

Periodic monitoring of white blood cell counts should be considered to permit detection of a possible leucopenia. 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.

Renal Function Monitoring

Use of ramipril should include appropriate assessment of renal function. Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.

INFORMATION FOR THE PATIENT

CARDIOVASCULAR

Hypotension

Patients should be cautioned to report lightheadedness, especially during the first few days of ramipril therapy. If actual syncope occurs, the patients should be told to discontinue the drug and consult with their physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure, patients should be advised to consult with their physician.

HEMATOLOGIC

Hyperkalemia and Potassium-Sparing Diuretics

Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia/Agranulocytosis

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**).

HEPATIC/BILIARY

Patients should be advised to return to their physician if they experience any symptoms possibly related to liver dysfunction. This would include "viral-like symptoms" in the first weeks to months of therapy (such as fever, malaise, muscle pain, rash or adenopathy which are possible indicators of hypersensitivity reactions), or if abdominal pain, nausea or vomiting, loss of appetite, jaundice, itching or any other unexplained symptoms occur during therapy.

IMMUNE

Angioedema

Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema, such as swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing. They should immediately stop taking ramipril and consult with their physician.

SPECIAL POPULATIONS

Pregnancy

Since the use of ramipril during pregnancy can cause injury and even death of the developing foetus, patients should be advised to report promptly to their physician if they become pregnant and the use of ramipril should be stopped.

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.

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= 1244), 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 CLINICAL TRIAL ADVERSE DRUG REACTIONS (<1%)
Clinical adverse events occurring in less than 1% of patients treated with ramipril in controlled clinical trials, or seen in postmarketing experience, are listed below by body system:

Body as a Whole: Anaphylactoid reactions, angioedema

Cardiovascular: Symptomatic-hypotension, syncope, angina pectoris, arrhythmia, chest pain, palpitations, tachycardia, myocardial infarction, cerebrovascular disorders (including ischemic stroke).

CNS: Anxiety, amnesia, confusion, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, polyneuritis, somnolence, tinnitus, tremor, vertigo, vision disturbances.

Dermatologic: Apparent hypersensitivity reactions (with manifestations of urticaria, pruritus, or rash, with or without fever), photosensitivity, purpura, erythema multiforms, pemphigus, Stevens-Johnson syndrome.

In addition, the following cutaneous or mucosal reactions may occur: exacerbation of psoriasis, maculo-papular exanthema, psoriasiform exanthema, pemphigoid exanthema and enanthema, and toxic epidermal necrolysis or onycholysis.

Gastrointestinal: Hepatic failure, cholestatic jaundice, hepatitis, pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, smell and taste disturbance, vomiting.

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.

Haematologic: Agranulocytosis, leucopenia, eosinophilia, thrombocytopenia, pancytopenia and hemolytic anemia.

Renal: Increases in blood urea nitrogen (BUN) and serum creatinine.

Respiratory: Increased cough.

Other: Arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, weight gain.

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leucocytosis. 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 hemoglobin or hematocrit; hyponatremia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

DRUG INTERACTIONS

DRUG-DRUG INTERACTIONS
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 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**).

Agents Increasing Serum Potassium: Since ramipril 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 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 coadministration 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: 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**)

Antidiabetic Agents (e.g. insulin and sulfonylurea derivates): ACE inhibitors may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycemic reactions in patients concomitantly treated with antidiabetics. Particularly close blood glucose monitoring is, therefore, recommended in the initial phase of coadministration.

DOSAGE AND ADMINISTRATION

RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

Essential Hypertension

Dosage of ramipril 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 may need to be adjusted.

Monotherapy:

The recommended initial dosage of ramipril 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 alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ramipril.

Concomitant Diuretic Therapy:
Symptomatic hypotension occasionally may occur following the initial dose of ramipril 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 to reduce the likelihood of hypotension (see **WARNINGS AND PRECAUTIONS**). If the diuretic cannot be discontinued, an initial dose of 1.25 mg ramipril should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ramipril should subsequently be titrated (as described above) to the optimal response.

Use in renal impairment:
For patients with a creatinine clearance below 40 mL/min/1.73m^2 (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg ramipril 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 10 mL/min/l.73m^2) the maximum total daily dose of 2.5 mg ramipril should not be exceeded.

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.

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

ACTION AND CLINICAL PHARMACOLOGY

MECHANISM OF ACTION
Ramipril is an angiotensin converting enzyme (ACE) inhibitor, which is used in the treatment of essential hypertension.

Following oral administration, ramipril 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**, **HEMATOLOGIC**, **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 l-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 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 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

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 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 angiotension 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 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 Ava-Ramipril in original container between 15 and 30^{o}C, protect from light and moisture and do not store beyond date indicated on the container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DOSAGE FORMS

1.25 mg tablet - white, oblong, flat tablet, debossed “R” and “1.25” on one side only.

2.5 mg tablet - white oblong, flat tablet, debossed “R” and “2.5” on one side only.

5 mg tablet - white, oblong, flat tablet, debossed “R” and “5” on one side only.

10 mg tablet - white, oblong, flat tablet, debossed “R” and “10” on one side only.

COMPOSITION

Ava-Ramipril tablets contain the following ingredients: Ramipril, sodium hydrogen carbonate, hypromellose, microcrystalline cellulose, pregelatinized starch and sodium stearyl fumarate.

PACKAGING

Ava-Ramipril is available in the following formats:
HDPE bottles of 100 tablets for all strengths.
HDPE bottles of 500 tablets for the strengths 2.5mg, 5mg and 10 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Ramipril

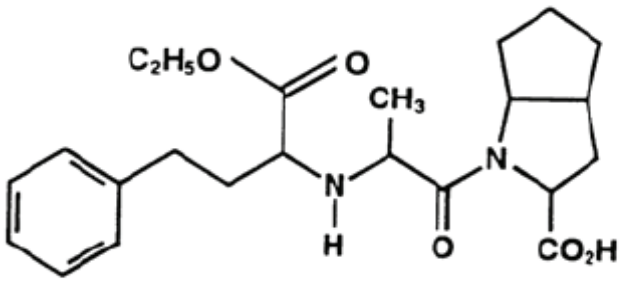
Chemical Name: 2-[N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1S,3S,5S)-2-azabicyclo-[3.3.0]octane-3-carboxylic acid

(2S, 3aS, 6aS)-1-[(S)-2-[[(S)-1-(ethoxycarbonyl)-3 phenylpropyl] amino] propanoyl] octahydrocyclopenta [b] pyrrole-2-carboxylic acid

Empirical Formula: $C_{23}H_{32}N_2O_5$

Molecular Mass: 416.52

Structural Formula:



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

Comparative Bioavailability Study

Single dose crossover comparative bioavailability study of ramipril 10 mg tablets *vs* Altace® 10 mg capsules in 40 healthy male volunteers (18 to 50 years old) was conducted under fasted conditions. Bioavailability data were measured and the results are summarized in the following table.

Table 1 – Single Dose Crossover Comparative Bioavailability Study of Ramipril 10 mg Tablets *vs* Altace® 10 mg Capsules in 40 Healthy Male Volunteers- Fasted Conditions.

Ramipril (1 x 10 mg) From measured data Uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test Ramipril 10 mg tablets**	**Reference Altace®†**	**% Ratio of Geometric Means**	**90 % Confidence Interval**
AUC_T (ng·h/mL)	15.717 17.977 (50.6)	14.452 16.221 (50.6)	108.75	99.03- 119.44
AUC_I (ng·h/mL)	16.202 18.437 (49.8)	15.047 16.886 (50.0)	107.68	97.94- 118.39
C_{MAX} (ng/mL)	16.861 19.934 (54.2)	20.052 23.768 (75.6)	84.08	70.14- 100.79
T_{MAX}* (h)	0.67 (0.25-1.25)	0.50 (0.33-1.25)		
$T_{½}$** (h)	1.15 (53.1)	1.67 (120.4)		

† Altace® is manufactured by Hoechst Marion Roussel and was purchased in Canada.
* Expressed as the median (range) only.
** Expressed as the arithmetic mean (CV %) only.

Single dose crossover comparative bioavailability study of ramipril 1.25 mg tablets *vs* Altace® 1.25 mg capsules in 42 healthy volunteers (8 females and 34 males), aged 18 to 50 years old, was conducted under fasted conditions. Bioavailability data were measured and the results are summarized in the following table.

Table 2 – Single Dose Crossover Comparative Bioavailability Study of Ramipril 1.25 mg Tablets *vs* Altace® 1.25 mg Capsules in 42 healthy volunteers (8 females and 34 males)- Fasted Conditions.

Ramipril (1 x 1.25 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test Ramipril 1.25 mg	Reference† Altace® Hoechst marion Roussel Canada Inc., Canada	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-t} (pg·h/mL)	2817.98 3033.38 (40.96)	2736.93 2968.62 (43.70)	102.96	96.85-109.46
AUC_{0-inf} (pg·h/mL)	2937.37 3167.03 (42.65)	2849.91 3104.28 (45.91)	103.07	96.87-109.67
C_{max} (pg/mL)	2589.54 2815.09 (41.59)	2751.25 3049.90 (50.42)	94.12	83.99-105.48
T_{max}§ (h)	0.667 (0.166)	0.500 (0.167)		
$T_{½}$ (h)	2.18 (37.57)	2.41 (58.31)		

† Identity of the reference product, including the manufacturer, and origin (country of purchase)
§ Expressed as the 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 more than 6 hours
Effect of pretreatment with ramipril on b.p. changes induced by IV 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 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 4: Effects on Blood Pressure

Hypertensive Model	Species	#/group	Route	Dose	Duration	Results
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 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 of radioactivity	0.5 hrs	0.5-l 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 23-42h	urine: 15% $t_{1/2}$: 9.3 h feces: 79% $t_{1/2}$: 8h	urine: 56% $t_{1/2}$: 7.2 and 127h feces: 40% $t_{1/2}$: 11 and 110 h

TOXICOLOGY

Acute Toxicity

Below are summarized species-specific LD_{50} values for both oral and intravenous 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 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 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 & 2500 mg/kg/d: Reduced heart weight. At 2500 mg/kg/d: Reduced erythrocytes, hematocrit and bilirubin, increased BUN.

Table 7 - Chronic Toxicity (continued)

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
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.
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, hemoglobin, 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.

Table 7 - Chronic Toxicity (continued)

Species	Duration	No. of animals per group	Route	Dose (mg/kg/day)	Effects
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.
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 leucopenia, 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 8 – 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 F 14 days before mating to end of lactation	At 50 and 500 mg/kg/d: Parents renal pelvis enlargement, offspring light brown discolouration of kidney tissue and dilatation of renal pelvis. At 500 mg/kg/d: Parents yellow white colouring 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 21of 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 colouring 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 colouration 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.
Monkey (Cynomolgus)	4-13F	5, 50, 500	Days 20- 25 of gestation	At all doses: No sign of teratogenesis. At 5 mg/kg/d: Two abortions, seven diarrhea, two vomiting, ten weight loss. At 50 mg/kg/d: One animal died, three abortions, seven diarrhea, two vomiting, ten weight loss. At 500 mg/kg/d: Three animals died, one abortion, four weight loss, four vomiting, four 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 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]AVA-RAMIPRIL
(ramipril tablets)

This leaflet is part III of a three-part "Product Monograph" published when Ava-Ramipril was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Ava-Ramipril. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
For Patients with High Blood Pressure
Your doctor has prescribed Ava-Ramipril, a medication that helps to control blood pressure.

Take your medication as instructed by your doctor.

Managing your lifestyle:
Keeping your blood pressure controlled
But 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 Ava-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:
Ava-Ramipril opens blood vessels to reduce blood pressure, like the way opening a hose reduces water pressure. It is not, however, a cure.

When it should not be used:
- You have had an allergic reaction to ramipril and/or any components of Ava-Ramipril tablets (see what are the important nonmedicinal ingredients) or to any other medication of the same group of medicines called ACE (angiotensin converting enzyme) inhibitors. (see **WARNINGS AND PRECAUTIONS**.)
- You are pregnant or breast feeding
- You have a history of a condition called angioedema (dysfiguring type of temporary swelling which can be hazardous) (see **SIDE EFFECTS**).

What the medicinal ingredient is:
ramipril

What the important nonmedicinal ingredients are:
Hypromellose, microcrystalline cellulose, pregelatinized starch, sodium hydrogen carbonate and sodium stearyl fumarate.

For a full listing of nonmedicinal ingredients see Part I of the Product Monograph.

What dosage forms it comes in:
Tablets 1.25 mg, 2.5 mg, 5 mg and 10 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Ava-Ramipril should not be used during pregnancy. If you discover that you are pregnant while taking ramipril, stop the medications and please contact your physician as soon as possible.

BEFORE you use Ava-Ramipril talk to your doctor or pharmacist if:

You are currently taking any other medications, whether on prescription or otherwise (see INTERACTIONS WITH THIS MEDICATION)?
You should not be taking salt substitutes, potassium supplements or potassium containing medicine without the advice of your doctor. If you have to undergo any dental or other surgery, inform the dentist or physician in charge that you are taking this medicine.

You suffer from any other condition?
The presence of other medical problems may affect the use of ramipril. If you have developed heart failure after a heart attack, you may have to limit your physical activities: before you begin exercising, be sure to consult with your doctor. Make sure you tell your doctor if you have any other medical problems, especially if you have diabetes, liver disease, kidney disease, heart or blood vessel disease.

You are pregnant, breast feeding or thinking of becoming pregnant?

Taking ramipril during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant while taking ramipril, stop the medication and report promptly to your doctor as soon as possible.It is possible that ramipril passes into breast milk. You should not breast feed while taking ramipril.

Remember
Use this drug as directed by your doctor. All drugs can have both helpful and harmful effects. Both depend on the person and his or her condition. This leaflet alerts you to some of the times you should call your doctor. Other situations, which cannot be predicted, can arise. Nothing in this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about Ava-Ramipril.

INTERACTIONS WITH THIS MEDICATION

Some drugs may have a negative effect on ramipril, or ramipril may have a negative effect on other drugs. If you are currently taking any other medications, whether on prescription or otherwise, inform your doctor or pharmacist. This is especially important if you are taking diuretics (water pills) or any other medication to reduce blood pressure which may add to the blood pressure lowering effect of ramipril.

Drugs that may interact with ramipril include also agents increasing serum potassium: such as potassium supplements. Salt substitutes or medicines which contain potassium. These should be used with caution.

PROPER USE OF THIS MEDICATION

Usual Dose:
It is important to take Ava-Ramipril at the same time every day as prescribed by your doctor.

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

For patients taking diuretics or with impaired kidney function: The recommended initial dosage of ramipril is 1.25 mg daily.

Missed Dose:
If you forgot to take your Ava-Ramipril tablet, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including ramipril, may cause side effects. After you have started taking ramipril, it is important that you tell your doctor at once about any unexplained symptom you might experience. Examples of this are unexplained fever, rash, itching, any sign of infection, viral-like symptoms, flu-like symptoms, coughing, sore throat, abdominal pain, loss of appetite, sad mood, jaundice, dizziness, fatigue, or nausea. These side effects may disappear once your system becomes used to the medication. If they persist, discuss this with your doctor. Your medication might have to be reduced or changed.

Dizziness or lightheadedness may occur after the first dose of this medicine. Make sure you know how you react to this medicine before you drive, operate machinery, or do anything requiring you to be alert. If fainting occurs after using ramipril, discontinue use and consult your doctor.

If you are suffering from excessive sweating, vomiting or diarrhea, this may cause you to lose too much water and lead to problems with low blood pressure. See your doctor.

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

Symptom/effect		Talk with your doctor or pharmacist		Stop taking ramipril and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Hypotension		✓	
	Swelling		✓	
	Heart Attack		✓	
	Cerebrovascular accident (CVA)		✓	
	Syncope(or fainting)			✓
	Angioedema/Intestinal Angioedema			✓

Angioedema is characterized by swollen mouth, lips, tongue, eyes, extremities, throat or difficulty in swallowing or breathing. Intestinal angioedema may also occur and is characterized by abdominal pain (with or without nausea or vomiting). **If you notice swelling or feel pain in these areas, inform your doctor immediately. You should also inform your doctor if you have an unexplained fever, rash or itching.**

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

HOW TO STORE IT

Store in original container between 15 and 30°C, protect from light and moisture and do not store beyond the date indicated on the container.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1 866-234-2345
Toll-free fax: 1 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be obtained by contacting the sponsor, Avanstra Inc., at: 1-855-708-3678
or
by written request at:
10761-25th NE, Suite 110, Building B,
Calgary, Alberta, Canada
T2C 3C2

or by e-mail at :
medinfo@avanstra.com

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