drug information perspectives

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Contents

RAMIPRIL

TRADE NAME: Altace, Apo-Ramipril, Ratio-Ramipril

CLASSIFICATION: Angiotensin converting enzyme inhibitor (ACEI), carboxyalkyldipeptide

ACTION:
The active metabolite, ramiprilat, reversibly and competitively inhibits angiotensin converting enzyme (ACE) in the circulation and tissues, which prevents the metabolism of angiotensin I to angiotensin II. Decreased levels of angiotensin II: (a) help prevent blood pressure (BP) elevation from vasoconstriction of smooth muscle and sympathetic outflow of norepinephrine, (b) decrease aldosterone secretion, with a resultant mild natriuretic effect, and a decrease in sodium and water retention, (c) reduce total peripheral resistance with improvement in cardiac output, (d) increase plasma renin activity by decreasing negative feedback on renal renin secretion, and (e) reduce trophic effects of angiotensin II on vascular smooth muscle and cardiac myocytes. Ramiprilat blocks the degradation of bradykinin by inhibiting kininase II (which is identical to ACE) and thereby promotes the release of endothelium-derived nitric oxide and vasodilatory prostaglandins, which may contribute to therapeutic and organ-protective effects, and possibly the pathogenesis of some adverse effects, the mechanisms of which have not been fully elucidated.
See also **ACTION** in **ANGIOTENSIN CONVERTING ENZYME INHIBITORS** monograph.

PHARMACOKINETICS:
Half-life: Triphasic elimination; half-life (distribution): 2-4 hours; half-life (apparent): 9-18 hours; half-life (terminal): >50 hours. Long terminal half-life due to high affinity to ACE-binding sites and slow dissociation of the ramiprilat-ACE complex.

Absorption: Bioavailability of 44-66%. Ingestion of food does not affect the extent, but may decrease the rate of absorption. Peak levels of ramipril and ramiprilat at 0.25-1 hour and 1.5-4 hours post-dose, respectively. Onset of action on BP: 1-2 hours; maximum reduction of BP: 3-6 hours.

Distribution: Plasma protein binding of ramipril and ramiprilat is 73% and 56%, respectively. Volume of distribution of 1.2L/Kg.

Metabolism: Extensive first-pass metabolism; rapid hepatic de-esterification to the active metabolite, ramiprilat. Further metabolized to inactive metabolites.

Elimination: 60% excreted in urine; 40% excreted in feces.

Special populations:
Elderly: Highly variable pharmacokinetics, unlikely to be clinically relevant; higher peak levels of ramiprilat.
Impaired hepatic function: Limited data; increased levels of ramipril, but not ramiprilat.
Impaired renal function: Higher peak, longer time to peak (6-8 hours), and slower decline of ramiprilat levels; reported terminal half-life of ramiprilat of up to 140 hours with creatinine clearance <15mL/min. Peak ramiprilat level and peak reduction in BP at 6 hours post-dose reported with creatinine clearance of 5-17mL/min.

USES AND EFFICACY:
Uses:
Essential hypertension; in congestive heart failure (CHF) (NYHA Functional Class II-IV) to slow disease progression, improve survival, exercise tolerance and quality of life, and reduce hospitalizations and incidence of recurrent myocardial infarction (MI); following acute MI (as soon as safely possible) for at least 6 weeks, and indefinitely in patients with left ventricular dysfunction (ejection fracture <40%) or evidence of CHF (even if only transient); in asymptomatic patients with moderate to severe left ventricular dysfunction (ejection fracture <35%); for cardiovascular protection in patients >55 years at high risk of cardiovascular events, in whom particular comorbid conditions exist (See **Place in Therapy**); renoprotection.

Major clinical trials:
The *Acute Infarction Ramipril Efficacy* (AIRE) Study was a multicentre, multinational, double-blind, placebo controlled study in 1986 patients with acute MI and clinical evidence of heart failure (patients with severe heart failure resistant to conventional therapy excluded) randomized within 3-10 days (mean 5.4 days) after acute MI to receive ramipril up to 5 mg twice daily or placebo. At an average of 15 months, the primary endpoint of all-cause mortality, based on survival curves, was significantly less in the ramipril group compared with placebo (27% reduction in overall mortality, p=0.002); incidence of severe heart failure, MI and stroke were significantly reduced. Long-term follow up showed sustained survival benefit over a mean of 59 months.

The *Heart Outcomes Prevention Evaluation* (HOPE) was a double-blind, randomized, placebo-controlled study conducted in 267 centres in 19 countries. Patients (55 years of age or older) with a history of coronary artery disease, stroke, peripheral vascular disease or diabetes, plus at least one other cardiovascular risk factor, and no evidence of left ventricular systolic dysfunction or heart failure were randomized to receive ramipril 10 mg daily (n=4645), ramipril 2.5 mg daily (n=244), or placebo (n=4652) for 5 years. The study was stopped at 4.5 years because of a significant improvement in outcome in patients receiving ramipril 10 mg daily; ramipril therapy significantly decreased the relative risk of the combined primary endpoint (MI, stroke, cardiovascular death) compared to placebo (p<0.001); the decrease in relative risk of each of the outcome components were all significant. Benefit of therapy was not attributable to reduction in BP as the majority of patients were not hypertensive at baseline and mean reduction of BP was extremely small. A similar beneficial effect was seen in both women and men. Analysis of data from the HOPE study revealed a lower rate of newly diagnosed diabetes in patients receiving ramipril. A pharmacoeconomic analysis of this study found treatment with ramipril to be cost-saving and resultant reduction of cardiovascular complications to be cost-effective. The *Heart Outcomes Prevention Evaluation-The Ongoing Outcomes* (HOPE-TOO) study, a post-trial follow-up of 2.6 years, revealed that benefits were maintained for reduction of cardiovascular death, stroke and hospitalization for heart failure; further reductions in rates of MI, need for revascularization and development of diabetes were reported, despite similar ACEI use and BP levels between the two study groups.

Place in therapy:

Hypertension:

- Antihypertensive efficacy is reduced in black patients, compared to other antihypertensive agents; not recommended as monotherapy in this population.
- Management guidelines from the Canadian Hypertension Society and National Institutes of Health (U.S.) indicate**:**
  - Ramipril (or another ACEI) is an appropriate agent in non-black patients for initial monotherapy of stage 1 hypertension (without compelling indications for the initial use of other antihypertensive therapy) as either a first-line drug (Canadian guidelines), or second-line alternative to thiazide diuretics (U.S. guidelines).
  - For combination therapy of stage 1 hypertension: (1) ramipril (or another ACEI), plus a thiazide diuretic, a long-acting calcium channel blocker (CCB), a beta blocker, or an angiotensin II receptor blocker (ARB) (Canadian guidelines); or (2) a thiazide diuretic for most patients, plus ramipril (or another ACEI), a CCB, an ARB, or a beta blocker (U.S. guidelines) are appropriate.
  - For combination therapy of stage 2 hypertension, a thiazide diuretic for most patients, plus ramipril (or another ACEI), a CCB, an ARB or a beta blocker are appropriate (U.S. guidelines).
  - For combination therapy of isolated systolic hypertension, a thiazide diuretic for most patients, plus ramipril (or another ACEI), a CCB, an ARB, or a beta blocker (U.S. guidelines) are appropriate.
  - Ramipril (or another ACEI) is one of the appropriate initial agents for the treatment of hypertension in patients with the following comorbid conditions: heart failure (in combination with a beta blocker and spironolactone), post-MI (in combination with a beta blocker), established coronary artery disease, diabetes (with or without nephropathy), chronic renal disease (in combination with a diuretic; avoid in the presence of bilateral renal artery stenosis or unilateral disease with a solitary kidney), left ventricular hypertrophy (LVH), and past cerebrovascular accident (CVA) or transient ischemic attack (in combination with a diuretic).

Congestive heart failure: An ACEI is the drug of choice for heart failure due to LV systolic dysfunction and is also of benefit in patients with asymptomatic LV systolic dysfunction; use of an adequate dose is important. An ARB is alternative therapy in patients intolerant of ACEIs; experienced clinicians may initiate combination ACEI and ARB therapy. Insufficient evidence exists to support triple therapy with an ACEI, an ARB, and a beta blocker. In a meta-analysis of 12 clinical trials of ACEI and beta blocker therapy, women with asymptomatic LV dysfunction did not show a reduction in mortality; further study required in this population. A retrospective cohort study showed no significant difference between enalapril, ramipril and lisinopril for patients with newly diagnosed CHF and rates of readmission for CHF or mortality. No prospective trials have compared ramipril with other ACEIs to assess survival benefit in patients with CHF.

Following acute myocardial infarction: An ACEI is the drug of choice and should be initiated as soon as safely possible; early initiation of therapy decreases left ventricular remodeling and is associated with faster recovery of left ventricular ejection fraction; particular benefit appears to occur in diabetic patients. An ARB is alternative therapy in patients intolerant of ACEIs. Two retrospective cohort studies have assessed the efficacy of the various ACEIs: one study in patients >65 years of age (n=7512) found that ramipril was associated with a lower mortality rate within the first year of hospital discharge post-acute MI compared to enalapril, fosinopril, captopril, quinapril and lisinopril{Pilote2004}; another study in patients >66 years of age (n=5408) showed no significant difference for the combined end-point of readmission for acute MI or mortality between patients receiving enalapril, ramipril, lisinopril, or other ACEIs. No prospective trials have compared ramipril with other ACEIs to assess survival benefit in patients following acute MI.

Cardiovascular protection: Clinical trials consistently demonstrate that control of BP reduces cardiovascular morbidity and mortality. Per unit fall in BP, the various antihypertensive agents are approximately as efficacious in producing these effects; no evidence of a special benefit of inhibition of ACE exists, other than that produced by BP reduction. An ACEI is recommended to decrease risk of MI, stroke or cardiovascular death in patients >55 years at high risk of cardiovascular events (coronary artery disease, stroke, peripheral artery disease, or diabetes plus at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol, low HDL,

cigarette smoking, or microalbuminuria). Reversal of LVH, an important independent risk factor for total mortality and for cardiovascular morbidity and mortality, appears to improve prognosis. Reduction of BP is an important component in the reversal of LVH. LVH is reduced more by ACEIs and ARBs than by other antihypertensive drug classes. Confirmation of a favorable effect of these agents on LVH in large studies will be of great importance to the future treatment of hypertension. The 2003 *Canadian Diabetes Association* (CDA) clinical practice guidelines suggest using an ACEI in combination with antiplatelet therapy (ASA) to reduce cardiovascular risk in all patients with diabetes.

Renoprotection: Although commonly utilized for this indication, the evidence for a specific renoprotective effect of ACEI therapy (or of combined therapy with an ACEI and an ARB) in diabetic and non-diabetic renal disease is weak. The quality of studies has been criticized due to small numbers of patients, short follow-up times, and endpoints being primarily surrogate markers such as proteinuria, not hard endpoints such as prevention of end-stage renal disease. The results of a meta-analysis of 127 studies assessing the renal effects of drugs which inhibit the renin-angiotensin system and other antihypertensive agents revealed no benefit in comparative trials of ACEIs or ARBs versus therapy with other antihypertensive agents, on doubling of creatinine, end-stage renal disease, glomerular filtration rate or creatinine amounts in patients with diabetic nephropathy. In placebo-controlled studies, greater benefit was seen with both ACEI or ARB therapy on all renal outcomes, but these benefits were interpreted as probable results of reduction of BP, rather than a particular effect of these agents; in five studies assessing the benefits of treatment of non-diabetic renal disease, benefit beyond that of reduction of BP was deemed to be uncertain.

Although further study is required to establish the renoprotective effects of ACEIs (as short-term therapy with ACEIs has been shown to decrease albuminuria and prevent worsening of nephropathy, but long-term benefits of therapy are unknown), the 2003 CDA guidelines for the treatment of diabetic nephropathy recommend, even in the absence of hypertension: (a) for type 1 diabetes: an ACEI, and (b) for type 2 diabetes: an ACEI or ARB for patients with a creatinine clearance >60mL/min, and an ARB for patients with a creatinine clearance <60mL/min. Combined treatment with both classes of agents may be considered.

Advantages:
- Therapeutic effect maintained with occasional noncompliance.
- Does not have a negative inotropic effect, cause reflex tachycardia, or adversely affect lipid profile or blood glucose levels.
- Abrupt withdrawal does not produce a rapid increase in BP.

Disadvantages:
- A bothersome dry persistent cough develops in some patients and may be secondary to an accumulation of bradykinin and prostaglandins; may disappear on withdrawal of therapy or dosage reduction. The incidence of this adverse effect among ACEIs appears similar. See **SIDE EFFECTS** in the **ANGIOTENSIN CONVERTING ENZYME INHIBITORS** and **RAMIPRIL** monographs
- Intolerance due to angioedema in some individuals.
- More expensive than some other antihypertensive agents, such as diuretics and beta blockers.

Investigational/Unapproved Indications:
Limited evidence suggests a possible role in: treatment of post-renal-transplant erythrocytosis, reduction of mitral regurgitation secondary to mitral valve prolapse, and reduction of cardiac death, acute MI or heart failure following invasive revascularization in patients with asymptomatic moderate left ventricular dysfunction.

CONTRAINDICATIONS AND PRECAUTIONS:
Contraindications:
- **Hypersensitivity** to ramipril or any component of the drug product.
- **History of ACEI-related or ARB-related angioedema.**
- **Symptomatic hypotension.**

Precautions:

- **Monitoring:** Monitor BP frequently for 24 hours upon initiation of therapy, then closely for 2 weeks, and after any increase in dosage of ramipril or diuretic; high-risk patients include those with ischemic heart or cerebrovascular disease (an excessive decrease in BP may cause MI or CVA), CHF with low systolic BP, severe salt/volume depletion, and those receiving dialysis or vigorous diuretic treatment. Measurement of baseline values of the following advised and to be repeated with dosage increase and periodically during long term therapy: BP, heart rate (HR), electrolytes (potassium and sodium especially important), creatinine, BUN, albumin, urinalysis with quantitative proteins, white blood cell count with differential (especially important in the presence of collagen vascular disease and/or renal disease); ALT in patients without liver disease; ALT, AST, ALP, and GGT in patients with cirrhosis and/or liver failure.

Additional monitoring of serum potassium recommended: when adding or discontinuing hyperkalemic agents (see **INTERACTIONS**), and in patients with heart failure receiving spironolactone, decreased renal function, type 2 diabetes, or age greater than 70 years.

- **Albumin Solution:** May contain pre-kallikrein activator that stimulates formation of bradykinin and other kinases, which are deactivated by ACE; in patients receiving enalapril, hypotension, tachycardia and dermal flushing reported; artificial colloid recommended for intravascular plasma volume expansion in patients receiving ACEIs.
- **Angina Pectoris (severe):** Theoretical increased risk of decrease in coronary perfusion.
- **Aortic Stenosis:** Theoretical increased risk of decrease in coronary perfusion.
- **CHF (severe, with or without associated renal insufficiency):** Excessive hypotension reported causing oliguria and/or progressive azotemia, and rarely, acute renal failure and/or death.
- **Hymenoptera venom administration:** Isolated reports of anaphylactoid reactions in patients receiving ACEIs, while receiving desensitization therapy.
- **Elderly:** May have greater sensitivity to BP lowering effects.
- **Hemodialysis:** Increases risk of hypotension; modify dosage based on BP. Anaphylactoid reactions, sometimes fatal, have occurred in patients dialyzed with high-flux membranes (ex. polyacrylonitrile); consider a different type of membrane, or change therapy to an ARB.
- **Hepatic dysfunction:** Baseline hepatic function tests suggested prior to starting therapy; use caution in pre-existing liver dysfunction.
- **Hyperkalemia:** Uncommon in normal renal function or absence of other risk factors; incidence of 11% in one study involving patients receiving ACEIs (most with hypertension plus diabetes and/or a variety of cardiovascular problems); increased risk with renal dysfunction (substantial risk with creatinine clearance <30mL/min), diabetes mellitus, decompensated CHF, volume depletion, advanced age, or concomitant use of potassium supplements or agents with the potential to cause hyperkalemia. If serum potassium ≥ 5.5 mmol/L, decrease dose; if also taking an ARB or an aldosterone-receptor blocker, or both, stop one drug and recheck potassium. Extra caution required in patients with cardiac conduction disorders. See **INTERACTIONS**.
- **Hyponatremia:** Increases risk of hypotension and renal ischemia; if cause is excessive diuresis, discontinue diuretic prior to initiation of ramipril therapy, replete volume, and correct electrolyte abnormalities; if due to hyperactivity of renin-angiotensin-aldosterone system, initiate therapy in low doses with short-acting ACEI (captopril) and monitor creatinine and BP.
- **Hypotension:** To decrease risk, consider withholding diuretic 2-3 days before starting ramipril. Symptomatic hypotension, which rarely causes ischemia or infarction, may occur after the first or second dose, or with an increase in dose; more likely in hyponatremia and/or hypovolemia, renal artery stenosis, cardiac failure, dietary salt restriction, dialysis, diarrhea, vomiting or history of postural hypotension.
- **Hypovolemia:** To minimize risk of hypotension and renal dysfunction, initiate ramipril in graduated doses when patient normovolemic or slightly volume overloaded. In patients who become hypovolemic and develop symptomatic hypotension or an increase in creatinine >30% from baseline, reduce dose of or hold diuretic for 1-2 days, rather than reduce dose of or hold ramipril.
- **LDL dextran sulfate apheresis:** Anaphylactoid reactions (rare) reported; withhold drug temporarily prior to each apheresis.

- Renal dysfunction: In patients with renal dysfunction who achieve control of BP, serum creatinine often increases by 30% or less above baseline; with normal volume and sodium intake, stabilization of serum creatinine occurs within 2-4 weeks. Hold or stop therapy if creatinine rises more than 30% from baseline in euvolemic patients. A short-acting ACEI (captopril) in reduced doses recommended for patients at high risk of renal dysfunction (cardiac failure, hypovolemia, and those with widespread atherosclerotic disease, peripheral vascular disease, solitary functioning kidney, existing renal dysfunction, hyponatremia, hypotension, and advanced age).

- Renovascular hypertension: Safety and efficacy not established; to avoid use in bilateral or unilateral renal artery stenosis (in the presence of a solitary kidney) due to risk of acute renal failure, which may be irreversible if renal ischemia leads to renal artery thrombosis.

- Report any unexpected or serious adverse reactions to Health Canada's adverse drug reaction monitoring program (toll free telephone 1-866-234-2345, toll free fax 1-866-678-6789).

PREGNANCY AND LACTATION:

Contraindicated during all trimesters of pregnancy. An epidemiologic study conducted to assess the association between administration of an ACEI during the first trimester of pregnancy (n=209) and the risk of congenital malformations, revealed a risk that was 2.7 times as great as the risk compared to exposure to other antihypertensive agents (n=202) or no exposure to antihypertensive agents (n=29,096). The increased risk was primarily due to increased risks of malformations of the cardiovascular and central nervous systems; a post hoc analysis revealed an increased risk of renal malformations. Captopril and enalapril have proven to be teratogenic when administered during the second and third trimester; following use of ACEIs during the second and third trimester, estimated morbidity rate is 10-20%; a summary of 85 pregnancies revealed a 13% perinatal mortality rate (6 stillbirths and 5 neonatal deaths).

Teratogenic effects and neonatal injury caused by ACEIs include hypotension, renal dysplasia, anuria, reversible or irreversible renal failure, prematurity, persistent patent ductus arteriosus, and neonatal or fetal death; anuria-associated oligohydramnios may cause intrauterine growth restriction, hypoplastic lung development, craniofacial deformities include defects of skull ossification and limb contractures.

If alternative therapy not possible, patient counseling and serial ultrasound examinations to assess fetal development and volume of amniotic fluid recommended; detailed ultrasonography and echocardiography at 18 weeks of gestation is recommended for women who have taken an ACEI during the first trimester. Discontinue therapy if oligohydramnios observed (which may not appear until the fetus has sustained irreversible injury), unless benefit to the mother is life-saving. Biophysical profiling, and non-stress and contraction stress testing may be useful. Enrollment in the Motherisk Study is encouraged. Newborns are very sensitive to ACEIs, likely due to relative immaturity of autoregulation of renal blood flow; those exposed in utero should be closely monitored for hypotension (which could produce a neurological deficit), oliguria, and hyperkalemia.

A single dose of 10 mg produced undetectable amounts of ramipril and metabolites in breast milk; the manufacturer does not recommended use in nursing mothers due to insufficient information. The American Academy of Pediatrics considers ACEIs to be compatible with breast feeding.

SIDE EFFECTS:

Frequency of occurrence, beyond that experienced with placebo, indicated in brackets. Hypotension and resultant dizziness, fatigue and headache usually appear soon after initiation of therapy. Withdrawal of therapy secondary to adverse reactions reported in 4.1-7.9% of patients.

Cardiovascular: Hypotension (0.4-6%); postural hypotension (0.8%); syncope (0.7%); angina pectoris (0.9%); MI (0.3%); CVA (0.1%); edema (0.2%); arrhythmia, palpitations, tachycardia (rare).

CNS: Dizziness/vertigo (1.7%); somnolence (1.7%); headache (0.4-2.4%; anxiety, amnesia, confusion, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, polyneuritis, tinnitus, tremor, vertigo, vision disturbances (rare).
Dermatologic: Rash (0.4-1.4%); erythema multiforme, urticaria, pruritus, maculo-papular exanthema, psoriasiform exanthema and enanthema, exacerbation of psoriasis, purpura, toxic epidermal necrolysis or onycholysis, increased sweating (rare); pemphigus (1 case); UVA-induced allergic photodermatitis (1 case in a welder); Stevens-Johnson syndrome (1 case); lichen planus pemphigoides (2 cases).
Endocrine/Metabolic: Increased blood glucose (rare); syndrome of inappropriate ADH secretion (1 case).
Gastrointestinal: Nausea/vomiting (1.1%-1.9%); diarrhea (0.7%); abdominal pain, anorexia, constipation, dry mouth, dyspepsia, dysphagia, gastroenteritis, increased salivation, smell and taste disturbance, belching, flatulence (rare); visceral angioedema (1 case); pancreatitis (2 cases).
Genitourinary: Impotence (1.5%); renal impairment (0.7%); increased BUN, increased creatinine, proteinuria (rare); acute renal failure (rare; elderly patients with CHF especially susceptible; usually reversible upon withdrawal of therapy).
Hematologic: Agranulocytosis, eosinophilia, leucopenia, pancytopenia, thrombocytopenia, hemolytic anemia, decreased serum erythropoietin (rare); Evans Syndrome (1 case); decreased hemoglobin or hematocrit (especially in renal transplant patients, likely dose-dependent, reversible in this population, withdrawal of therapy rarely required).
Hepatic: Elevations of liver enzymes (ALT, AST, LDH) (rare, mostly reversible on discontinuation, cross sensitivity between ACEIs reported); hepatitis (3 cases, with 2 patients developing jaundice); biliary cirrhosis (1 case).
Hypersensitivity: Anaphylactoid reaction (rare); angioedema (0.1-0.2%; about 5 and up to 4.5 times the incidence in Hispanics and blacks compared to Caucasians, respectively; usually occurs within the first month of therapy, however may occur following years of use; usually subsides after 24-48 hours of stopping therapy); symptom complex (arthralgia, arthritis, myalgia, fever, vasculitis, positive ANA, elevated ESR, eosinophilia, leucocytosis (rare).
Neuromuscular: Arthritis (1.1%); arthralgia, myalgia (rare); concurrent arthralgia and myalgia (1 case).
Respiratory: Cough (3.9-5.5% increased incidence reported, but likely much higher in women, older women and Caucasians); dyspnea (1.1%); epistaxis (rare).
Other: Weight gain, symptomatic hyponatremia (increased risk in elderly), hyperkalemia, hyponatremia (rare).

INTERACTIONS:
No drug interaction reported when coadministered with acenocoumarol, antacids, digoxin, felodipine, furosemide, hydrochlorothiazide, or warfarin.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Anesthetics	Increased hypotensive effect	Suppression of renin-angiotensin system	Caution
Antiotensin II Receptor blockers	Hypotension, hyperkalemia, Worsening renal function	Additive effect	Caution; monitor closely if administered concurrently
Azathioprine	Increased risk of: leucopenia with captopril; anemia (may be severe) with captopril or enalapril (conflicting data)	Possibly additive bone marrow suppression by azathioprine and suppression of erythropoietin by ACEIs	Caution; monitor blood work

Capsaicin (topical)	Cough (1 case report)	Unknown	Caution
Cyclosporine	Nephrotoxicity (reported with enalapril or captopril)	Unknown	Caution
Diuretics	Excessive reduction of BP, especially with first 1 to 2 doses of ramipril or high doses of diuretics	Hypovolemia and sodium depletion	Caution; see DOSING
	Renal impairment (uncommon)	Diuretic-induced sodium depletion	Caution; monitor renal function
Erythropoietin	Increased requirement of erythropoietin in hemodialysis and peritoneal dialysis patients	Decreased erythropoietin secretion or inhibition of erythropoiesis	Caution; monitor hematocrit
Hypoglycemic agents (insulin, sulphonylureas)	Possible hypoglycemic reaction, especially with initiation of coadministration	ACEIs may reduce insulin resistance	Caution; monitor serum glucose
Lithium	Increased lithium level Causing neurotoxicity, nephrotoxicity	Increased reabsorption of of lithium; interaction at cellular level	Caution; monitor lithium level and renal function
NSAIDS (especially indomethacin, possibly ASA dose >100 mg daily, possibly COX-2 inhibitors) (conflicting data)	Decreased antihypertensive effect in some patients, decreased renal function (rare), hyperkalemia (rare)	Inhibition of renal prostaglandin synthesis, sodium and fluid retention	Caution; monitor BP when adding or stopping a NSAID, monitor renal function
Potassium-sparing diuretics (amiloride), triamterene, spironolactone	Increased serum potassium, hyperkalemia, especially in renal dysfunction	Additive effect	Caution; monitor potassium level often
Potassium supplements	Increased serum potassium, hyperkalemia, especially in renal dysfunction	Additive effect	Caution; unlikely needed; monitor potassium level often

Sirolimus	Tongue edema (5 case reports)	Unknown	Caution
	Acute, severe, allergic reaction (2 case reports; one with ramipril, one with enalapril)	Unknown	Caution
Trimethoprim	Increased serum potassium (rare), but potentially life-threatening; risk increased in elderly with chronic renal dysfunction and patients with AIDS receiving high dose cotrimoxazole	Additive effect	Caution; monitor potassium level

DOSAGE:

Adults:

Essential Hypertension: Recent treatment with other agents, and extent of elevation of BP and salt restriction must be considered; dosage of agents used concurrently may require adjustment. In patients receiving a diuretic, consider holding diuretic therapy for 2-3 days prior to starting ramipril. Initial dose 1.25-2.5 mg daily in one or two divided doses; initial dose 1.25 mg daily recommended with concurrent diuretic administration, or in the presence of fluid or salt depletion, or renovascular hypertension. Increase dose gradually every two weeks according to BP; usual maintenance dose 2.5-20 mg daily in one or two divided doses. Evaluate BP just prior to daily dose; if not controlled, increase dose or consider twice daily administration. Consider addition of a diuretic if BP remains uncontrolled; may reduce ramipril dose after addition of diuretic.

Heart failure: Initial dose 1.25 mg twice daily; target dose 5 mg twice daily; maximum dose 10 mg twice daily. Dosage reduction may be required with initiation of beta blocker therapy, then dose may be titrated up again.

Following Acute Myocardial Infarction: 2.5 mg twice daily; initiate 3-10 days following acute MI in hemodynamically stable patients with clinical signs of heart failure. Monitor patient for at least 2 hours and until BP stable for at least 1 additional hour. If hypotension occurs, fluid or salt depletion present, or concurrent diuretic administration, decrease to 1.25 mg twice daily. Increase by doubling every 1-3 days, to maximum 5 mg twice daily or 10 mg daily.

Reduction of the risk of myocardial infarction, stroke or death in patients at increased risk of cardiovascular events: Initial dose 2.5 mg daily for one week; if tolerated, increase to 5 mg daily for three weeks; if tolerated, increase to 10 mg daily (may be given in divided doses).

Elderly: Initial dose 1.25 mg daily; titrate as tolerated.

Children: 0.05 mg/Kg daily, may increase to 0.1-0.2 mg/Kg daily over 4-6 weeks.

Hypertension and renoprotection: 1.5-6 mg/m^2 daily has been studied in 2-19 year old patients with various nephropathies.

Renal impairment: Insufficient data for recommendations in severe renal failure.

Hypertension: Creatinine clearance <40mL/min/1.73m^2: Initial dose 1.25 mg daily; titrate slowly until BP controlled or maximum daily dose 5 mg daily with creatinine clearance 10-40mL/min/1.73m^2, or 2.5 mg daily with creatinine clearance <10mL/min/1.73m^2.

Following Acute Myocardial Infarction: Creatinine clearance 20-50mL/min/1.73m^2: Initial dose 1.25 mg daily; titrate slowly to maximum dose 1.25 mg twice daily.

Hepatic impairment: Reduce dose and monitor carefully.

NURSING IMPLICATIONS:

Ramipril may be given with food or on an empty stomach. If the patient has difficulty swallowing, open the capsule and mix contents with water, apple juice or applesauce; these mixtures are stable 24 hours at room temperature or 48 hours refrigerated.

Following the initial dose, addition of a diuretic, or a dosage increase, monitor BP and HR frequently. With chronic therapy, measure BP prior to each dose. If hypotension occurs, place patient in a supine position and elevate legs. Notify physician if marked hypotension occurs. Oral or IV fluids may be needed for volume repletion.

Urinalysis with quantitative protein determination and white blood cell counts with differential are recommended prior to starting the drug and periodically throughout long–term therapy.

Therapeutic outcome measurements in heart failure include improvement in symptoms (decreased dyspnea on exertion, paroxysmal nocturnal dyspnea or orthopnea), improved exercise tolerance, and decreased crackles and pedal edema.

Angioedema is a rare but potentially serious side effect. If swelling of the face, tongue, extremities, or larynx occur, discontinue drug and treat as required.

Patient compliance with antihypertensive medications is sometimes poor. Emphasize the importance of taking the medication regularly.

PATIENT INSTRUCTIONS:

Ramipril (ra mi' pril) is used to treat high blood pressure or heart failure, or to prevent heart attacks and strokes after a recent heart attack or if there is increased risk of developing these problems. Your physician may have prescribed this medication for other reasons.

Ramipril may be taken with or without food, and should be taken at about the same time every day. If it causes stomach upset, take it with food. If there is difficulty in swallowing the medication, open the capsule and mix the contents with applesauce, apple juice, or water, and then swallow it. These mixtures are stable 24 hours at room temperature or 48 hours refrigerated. Preparation just before a dose is preferable.

Take the medication exactly as prescribed by your physician. It must be taken regularly to be fully effective, even if you feel perfectly well. Always keep an adequate supply on hand.

If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, omit the missed dose and continue with your regularly scheduled one. Do not take a double dose to make up for the missed dose.

If you are taking this medication for high blood pressure, do not take medications that may increase blood pressure, such as non-prescription medications for appetite control, asthma, colds, cough, hay fever or sinus problems. Consult with your physician or pharmacist before taking any non-prescription medications.

Do not take salt substitutes or supplements containing potassium salts without your physician's recommendation because an accumulation of potassium may occur in your body.

Lightheadedness or dizziness may occur after the first few doses of this medication or after a dosage increase, especially if you have been taking a diuretic (water pill). If this occurs, lie or sit down until the symptoms pass. If fainting occurs, consult your physician before taking any more doses. Do not drive a motor vehicle or operate dangerous machinery until you know how this medication affects you. An excessive fall in blood pressure causing dizziness or fainting may occur if you become dehydrated due to excessive perspiration, vomiting or diarrhea; make sure you replace fluids lost from your body if these conditions occur.

If swelling of the face, mouth, hands or feet occurs, stop taking the medication and contact your physician. If swelling of the tongue or throat occurs, seek medical help immediately, as breathing difficulties may develop. These are symptoms of a rare reaction, which is a medical emergency.

Inform your physician if you experience persistent dizziness or headache, skin rash, taste disturbances, signs of infection (e.g. sore throat, fever, swollen glands), joint or muscle pain, or any other persistent or annoying side effect. Side effects are usually reversible if the medication is discontinued, or if the dose is reduced.

Some patients may develop a dry cough that may continue, disappear over time, or be relieved by dosage reduction. If the cough is persistent or bothersome, inform your physician. Be aware that increased coughing, especially at night, may be a symptom of worsening heart failure.

Stay in close contact with your physician so that he/she may follow how well this medication works for you.

This medication should usually not be taken during pregnancy. If you are planning a pregnancy, discuss this with your physician. If you may be pregnant, stop taking the drug and contact your physician.

Store this medication in a labeled container, away from heat, light and moisture, and out of the reach of children.

If you have experienced an unexpected or serious reaction to this medication, this can be reported to Health Canada’s monitoring program (toll free telephone 1-866-234-2345, toll free fax 1-866-678-6789). Note that this is not an emergency number.

PRESENTATION:
Capsules: 1.25, 2.5, 5 and 10 mg.

References are available on request.