PRODUCT MONOGRAPH

[Pr] RAMIPRIL-HCTZ

(ramipril and hydrochlorothiazide Tablets)

Tablets
5 mg ramipril/12.5 mg hydrochlorothiazide
10 mg ramipril/12.5 mg hydrochlorothiazide
10 mg ramipril/25 mg hydrochlorothiazide

Angiotensin converting enzyme inhibitor plus diuretic

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Date of Preparation:
November 6, 2013

Submission Control No.: 169338

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[Pr]RAMIPRIL-HCTZ
(ramipril/hydrochlorothiazide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non medicinal Ingredients
Oral	Tablet / -5 mg ramipril/12.5 mg hydrochlorothiazide -10 mg ramipril/25 mg hydrochlorothiazide -10 mg ramipril/25 mg hydrochlorothiazide	*Lactose Monohydrate* *For a complete listing, see Dosage Forms, Composition and Packaging section*

INDICATIONS AND CLINICAL USE

RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom this combination therapy is appropriate.

RAMIPRIL-HCTZ is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION). Patients in whom ramipril and diuretic are initiated simultaneously can develop symptomatic hypotension.

Patients should be titrated on individual drugs. If the fixed combination represents the dose and dosing frequency determined by this titration, the use of RAMIPRIL-HCTZ may be more convenient in the management of patients. If during maintenance therapy dosage adjustment is necessary it is advisable to use the individual drugs.

In using RAMIPRIL-HCTZ consideration should be given to the risk of angioedema (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Immune, Angioedema)

Geriatrics
There is limited clinical experience with RAMIPRIL-HCTZ in the elderly (> 65 years) (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Pediatrics
The safety and effectiveness of RAMIPRIL-HCTZ in children have not been established; therefore use in this age group is not recommended (see WARNINGS AND PRECAUTIONS, Special populations, Pediatrics).

CONTRAINDICATIONS

RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) is contraindicated in:

- patients who are hypersensitive to this drug, to any other angiotensin converting enzyme (ACE) inhibitor, or to any ingredient in the formulation (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

Because of the ACE inhibitor component, ramipril, RAMIPRIL-HCTZ is contraindicated in:

- patients who have a history of angioedema (see WARNINGS AND PRECAUTIONS, Angioedema).
- during pregnancy and in breast feeding-women (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women/Nursing Women)

Because of the hydrochlorothiazide component, RAMIPRIL-HCTZ is contraindicated in:

- patients with anuria or hypersensitivity to thiazides and other sulfonamide-derived drugs (see WARNINGS AND PRECAUTIONS, Immune, and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions, Immune).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

General

Angioedema

Angioedema has been reported in patients treated 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 AND HYDROCHLOROTHIAZIDE (TABLETS) 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.

Angioedema, including laryngeal edema, may occur especially following the first dose of ramipril and hydrochlorothiazide (tablets). 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 hydrochlorothiazide (tablets) and consult with their physician.

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 (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions, Immune)

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).

Cough
A dry, persistent cough, which usually disappears only after withdrawal of ramipril and hydrochlorothiazide (tablets), has been reported. This is likely related to ramipril, the ACE inhibitor component of ramipril and hydrochlorothiazide (tablets). Such a possibility should be considered as part of the differential diagnosis of cough (see ADVERSE REACTIONS, Clinical Trials Adverse Drug 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, Cardiovascular, Hypotension). Because of the potential fall in blood pressure in these patients, therapy with ramipril and hydrochlorothiazide (tablets) 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 and hydrochlorothiazide (tablets) 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 hydrochlorothiazide (tablets) should be considered. In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ramipril and hydrochlorothiazide (tablets) (see ADVERSE REACTIONS, Cardiovascular, Hypotension).

Ramipril and hydrochlorothiazide (tablets) may lower the state of patient alertness and/or reactivity, particularly at the start of treatment. Patients should be cautioned to report lightheadedness, especially during the first few days of ramipril and hydrochlorothiazide (tablets) 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

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ramipril cannot be excluded (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). 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, Hematological Monitoring).

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

HepaticBiliary

Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions). In most cases the changes were reversed on discontinuation of the drug.

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.

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 (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Should the patient receiving ramipril and hydrochlorothiazide (tablets) 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 and hydrochlorothiazide (tablets) should be considered when appropriate.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ramipril and hydrochlorothiazide (tablets) should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Immune

Anaphylactoid Reactions to ACE Inhibitors

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.

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.

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.

Hypersensitivity to Thiazide Diuretics

Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

Metabolism

Thiazides, including HCT, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia, and hypochloremic alkalosis).

Hyperuricemia may occur, or acute gout may be precipitated, in certain patients receiving thiazide therapy.

Thiazides may decrease serum PBI (protein-bound iodine)levels without signs of thyroid disturbance.

Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests of parathyroid function.

Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy.

Dosage adjustments of insulin or oral hypoglycemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Administration of ACE inhibitors in patients with diabetes may potentiate the blood glucose lowering effect of oral hypoglycemic agents or insulin (see DRUG INTERACTIONS, Drug-Drug Interactions).

Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with the ACE inhibitor ramipril. In most cases these were isolated values which resolved despite continued therapy. 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, Agents increasing serum potassium).

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

Peri-Operative Considerations

Surgery/Anesthesia

In patients undergoing surgery or anesthesia with agents producing hypotension, ramipril and hydrochlorothiazide (tablets) 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.

Thiazides may increase the responsiveness to tubocurarine .

Patients planning to undergo surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

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 and hydrochlorothiazide (tablets) should include appropriate assessment of renal function.

Ramipril and hydrochlorothiazide (tablets) 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 (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Renal Function Monitoring).

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 mL/min or below (i.e., moderate or severe renal insufficiency).

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

Special Populations

Pregnant Women
ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ramipril and hydrochlorothiazide (tablets) should be discontinued as soon as possible.

In rare cases (probably less than one in every thousand pregnancies) in which no alternative to ACE inhibitor therapy will be found, the mother(s) should be apprised of the potential hazard(s) to their foetus(es). Serial ultrasound examinations should be performed to assess fetal development and well-being and the volume of amniotic fluid.

If oligohydramnios is observed, ramipril and hydrochlorothiazide (tablets) should be discontinued unless it is considered life-saving for the mother. A non-stress test (NST), and/or a biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. If concerns regarding fetal well-being still persist, a contraction stress testing (CST) should be considered. Patients and physicians should be aware, however, that oligohydramnios may not appear until the foetus has sustained irreversible injury.

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.

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

Human Data: It is not known whether exposure limited to the first trimester of pregnancy can adversely affect fetal outcome. 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; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and

hypoplastic lung development. Prematurity and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

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
Ingestion of a single 10 mg oral dose of ramipril resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses and because thiazides do appear in human milk, ramipril and hydrochlorothiazide (tablets) should not be administered to nursing mothers (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Nursing Women).

Pediatrics
The safety and effectiveness of ramipril and hydrochlorothiazide (tablets) in children have not been established; therefore use in this age group is not recommended.

Geriatrics
Because of decreased cardiovascular reserve, greater sensitivity in older patients (> 65 years) may be expected.

Monitoring and Laboratory Tests

Hematology
Periodic monitoring of white blood cell counts should be considered to permit detection of a possible leukopenia due to ACE inhibitor component of ramipril and hydrochlorothiazide (tablets), ramipril. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma) or those treated with other drugs that can cause changes in the blood picture (see WARNINGS AND PRECAUTIONS, Hematologic, Neutropenia/Agranulocytosis).

Metabolism
Appropriate monitoring of electrolytes and blood sugar is required.

Renal Function
Use of ramipril and hydrochlorothiazide (tablets) 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 (see WARNINGS AND PRECAUTIONS,Renal).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent adverse drug reactions observed with ramipril/hydrochlorothiazide were: headache (3.9%), dizziness (2.2%) and bronchitis (2.1%). The common serious adverse event pooled from the different clinical trials was tachycardia (0.2%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug 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

Table 1 – Adverse Events occurring ≥ 1% in patients taking ramipril + HCT in controlled clinical trials

Adverse Events	Ramipril+HCT* n= 967 (%)	Ramipril n= 1058 (%)	HCT n= 515 (%)	Placebo n= 44 (%)
Headache	3.9	1.7	6.0	4.5
Dizziness	2.2	1.5	1.0	4.5
Bronchitis	2.1	0.5	0.4	0.0
Neuralgia	1.9	0.4	0.4	2.3
Infection	1.8	0.4	1.2	2.3
Upper respiratory infection	1.4	0.4	0.8	2.3
Asthenia	1.3	1.3	1.6	2.3
Cough increased	1.3	1.2	1.0	0.0
Back pain	1.0	0.6	0.6	0.0

*: Patients taking ramipril + hydrochlorothiazide in combination.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Body as a whole: allergic reactions, fever, shock.

Cadiovascular system: angina pectoris, hypotension, palpitation, postural hypotension, syncope, tachycardia.

Digestive system: constipation, gastroenteritis, gastrointestinal pain, nausea.

Metabolic and nutritional disorders: excessive thirst, gout, hyperglycemia, hyperuricemia, hypokalemia and peripheral edema.

Musculo-skeletal system: arthralgia, myalgia,.

Nervous system: anxiety, apathy, depression, dry mouth, hot flushes, nervousness, paresthesia, sleep disorder, somnolence, sweating and tremor.

Respiratory system: dyspnea, and sinusitis.

Skin and appendages: alopecia, angioedema, maculopapular rash, pruritus, psoriasis, rash.

Special senses: conjunctivitis, taste loss, and tinnitus. **Urogenital system:** impotence, renal

failure, kidney function abnormal.

Abnormal Hematologic and Clinical Chemistry Findings

Hydrochlorothiazide

Renal function test: increased serum concentrations of uric acid.

Cholesterol: increase in serum cholesterol and triglycerides.

Glucose: lower tolerance to glucose. In patients with diabetes mellitus, this may lead to a deterioration of the metabolic control.

Post-Market Adverse Drug Reactions

Cardiovascular: tachycardia, palpitations, disturbed orthostatic regulation, hypotension, asthenia, angina pectoris, cardiac arrhythmias, syncope, myocardial infarction, ischaemic stroke and peripheral oedema.

Central Nervous System: headache, disorders of balance, weakness and light-headedness, dizziness, tinnitus, paraesthesiae, nervousness, depressed mood, tremor, restlessness, confusion, feeling of anxiety, transient erectile impotence, sweating and somnolence.

Dermatologic: cutaneous or mucosal reactions such as rash, pruritus or urticaria, maculopapular rash, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia or photosensitivity, pemphigus, exacerbation of psoriasis, psoriasiform or pemphigoid exanthema and enanthema, or onycholysis.

Endocrine and Metabolism: decline in serum sodium concentration, hypochloraemia, hypomagnesaemia, hypercalcaemia, development or aggravation of a metabolic alkalosis, increase in the concentration of serum potassium due to ramipril, decrease in potassium concentration due to hydrochlorothiazide. General signs of disturbances in the electrolyte balance: headache, drowsiness, confusion and muscle cramps. Increased fluid excretion.

Gastrointestinal: vasculitis, nausea, increases in serum levels of hepatic enzymes and/or bilirubin, cholestatic and jaundice, dryness of the mouth, glossitis, inflammatory reactions of the oral cavity and gastrointestinal tract, abdominal discomfort, gastric pain (including gastritic-like gastric pain), digestive disturbances, smell and taste disturbances, constipation, diarrhea, vomiting, increased levels of pancreatic enzymes, pancreatitis, liver damage (including acute liver failure).

Genitourinary: increase in serum urea and serum creatinine and impairment of renal function, progression to acute renal failure, interstitial nephritis and pre-existing proteinuria may deteriorate (though ACE inhibitors usually reduce proteinuria), reduced libido, transient erectile impotence.

Hematologic: hematological reactions to ACE inhibitors are more likely to occur in patients with impaired renal function and in those with concomitant collagen disease (e.g., lupus erythematosus or scleroderma) or in those treated with other drugs that may cause changes of the blood picture (see WARNINGS AND PRECAUTIONS, Hematologic, and DRUG INTERACTIONS). Haemolytic anaemia, reduction in the white blood cell or blood platelet count, agranulocytosis, pancytopenia and bone marrow depression.

Immune: fever, eosinophilia, angioedema and other, not pharmacologically mediated anaphylactic or anaphylactoid reactions to ramipril or any of the other ingredients are rare (see WARNINGS AND PRECAUTIONS, Immune). Anaphylactic reactions to hydrochlorothiazide are possible. The likelihood and the severity of anaphylactoid reactions to insect venoma are increased under ACE inhibition.

Musculoskeletal: myalgia, arthralgia, muscle cramps develop

Respiratory: dry (non-productive) tickling cough, nasal congestion, sinusitis, bronchitis, bronchospasm and dyspnoea.

Special Senses: visual disturbances, disturbed hearing.

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

Table 2- Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Concomitant Diuretic Therapy	CT	Hypotensive effects	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 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	CT	Elevation of 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	T	Antihyperten-sive effect augmented	The antihypertensive effect of ramipril is augmented by antihypertensive agents that cause renin release.
Lithium	CT	Increased serum lithium levels and symptoms of lithium toxicity	Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors and thiazides during therapy with lithium. If these drugs must be used together, decrease lithium dose by 50% with close monitoring of lithium concentration, serum electrolytes and fluid intake. 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.

Table 2 (Continued)- Established or Potential Drug-Drug Interactions			
Antacids	CT	No effect.	In one open-label, randomized, cross-over single dose study in 24 male subjects, it was determined that the bioavailability of ramipril and the pharmacokinetic profile of ramiprilat were not affected by concomitant administration of the antacid, magnesium and aluminum hydroxides.
Digoxin:	CT	No changes in serum levels of ramipril, ramiprilat, and digoxin with ramipril intake.	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.
		Thiazide-induced electrolyte disturbances (mainly hypokalemia and hypomagnesemia) increase risk of digoxin toxicity.	Clinical significance of digoxin toxicity with thiazides is high. Monitor serum electrolytes, particularly potassium and magnesium levels. Administer potassium and/or magnesium supplements as required.
Warfarin		No alteration of the anticoagulant effects with ramipril.	The co-administration of ramipril with warfarin did not alter the anticoagulant effects.
Acenocoumarol	CT	No significant change in blood pressure, thrombotest time and coagulation factors with ramipril.	In a multi-dose double-blind, placebo-controlled, pharmacodynamic interaction study with 14 patients with mild hypertension administered both ramipril and therapeutic doses of acenocoumarol, blood pressure, thrombotest time and coagulation factors were not significantly changed.

Table 2 (Continued)- Established or Potential Drug-Drug Interactions			
Non-steroidal anti-inflammatory agents	CT	Increased risk of worsening of renal function and an increase in serum potassium. Possible attenuation of the diuretic, natriuretic, and antihypertensive effects.	The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of non-steroidal anti-inflammatory agents (e.g. indomethacin). Concomitant treatment with 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) Avoid if possible. If not possible, close monitoring of serum creatinine, potassium and patient's weight is recommended if using NSAIDs with ALTACE® HCT (ramipril/hydrochlorothiazide). Observe the patient to ensure diuretic effects are obtained. Monitor blood pressure and diuretic effect and increase dose if necessary or discontinue NSAID. Also monitor renal function.
Antidiabetic agents (e.g. insulin and sulfonylurea derivates)	CT	Hypoglycemic reactions with ACE inhibitors. Hyperglycemic reactions with thiazides.	ACE inhibitors drugs may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycaemic reactions in patients concomitantly treated with antidiabetics. Particularly close blood glucose monitoring is, therefore, recommended in the initial phase of co-administration. Clinical significance is minimal to moderate but likely. Effect may occur after several days to several months of therapy. Monitor for changes in glycemic control and ensure adequate potassium levels are maintained. Supplement potassium and/or adjust dose of antidiabetic medications if required.

Table 2 (Continued)- Established or Potential Drug-Drug Interactions			
Skeletal muscle relaxants (Curare type)	T	Thiazide drugs may enhance the effects of nondepolari-zing skeletal muscle relaxants	Thiazides may enhance the effects of nondepolarizing skeletal muscle relaxants potentially leading to prolonged respiratory depression. Thiazide-induced hypokalemia increases resistance to depolarization by hyperpolarizing the end plate resulting in enhanced myoneural blockade. Monitor and correct thiazide-induced hypokalemia. Consider decreasing dose of nondepolarizing skeletal muscle relaxant if hypokalemia cannot be corrected before administration of muscle relaxants is required. Clinical significance is unknown.
Sympathomimetics	T	Reduce the antihypertensive effect.	May decrease antihypertensive effect. May decrease arterial responsiveness to norepinephrine but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Clinical significance is unknown.
Alcohol, barbiturates, narcotics	T	Orthostatic hypotension	Orthostatic hypotension may occur. Alcohol, barbiturates and narcotics may potentiate the antihypertensive effects. Avoid alcohol, especially with initiation of therapy (see WARNINGS AND PRECAUTIONS).
Corticosteroids	T	Possible hypokalemia. Possible reversal of thiazide antihyperten-sive response via cortico-steroid-induced salt and water retention.	Monitor serum potassium levels and replace potassium if required. Monitor blood pressure and adjust medications as required.
Legend: T = Theoretical, CT= Clinical Trial			

Drug-Food Interactions

No substantial drug-food interaction has been detected with ramipril or hydrochlorothiazide.

Drug-Laboratory Test Interactions

Tests for Parathyroid Function

Hydrochlorothiazide stimulates renal calcium reabsorption and may cause hypercalcemia. This must be considered when carrying out tests for parathyroid function.

Drug-Lifestyle Interactions

No information available.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Dosage should be individualized.
- RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) is not for initial therapy.
- The dose of RAMIPRIL-HCTZ should be determined by the titration of the individual components.
- Special attention for dialysis patients.

Recommended Dose and Dosage Adiustment

Once the patient has been successfully titrated with the individual components as described below, RAMIPRIL-HCTZ may be substituted if the titrated dose and dosing schedule can be achieved by the fixed combination (see INDICATIONS AND CLINICAL USE, and WARNINGS AND PRECAUTIONS).

Usual dosage: 2.5 mg ramipril and 12.5 mg hydrochlorothiazide (corresponding to 1 tablet RAMIPRIL-HCTZ 2.5/12.5) daily. Generally it is recommended that the daily dose be administered in the morning as a single dose.

Titration will be based on physician's judgement according to severity of hypertension and other associated risk factors.

Maximum daily dose: 10 mg ramipril and 50 mg hydrochlorothiazide (corresponding to 4 tablets RAMIPRIL-HCTZ 2.5/12.5 or 2 tablets RAMIPRIL-HCTZ 5/25).

Dosage in patients with impaired renal function

Creatinine clearance 30 to 60 ml/min per 1.73 m^2 body surface area: the maximum recommended daily dose for renally impaired patients is 5 mg ramipril/25 mg hydrochlorothiazide (corresponding to 2 tablets RAMIPRIL-HCTZ 2.5/12.5 or 1 tablet RAMIPRIL-HCTZ 5/25).

Missed Dose
If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

Administration
RAMIPRIL-HCTZ tablets should be swallowed with sufficient amounts of liquid (approximately glass). The tablets must not be chewed or crushed.

Generally, it is recommended that the daily dose be administered in the morning as a single dose. No substantial food effects is to be expected with RAMIPRIL-HCTZ.

OVERDOSAGE

For the management of suspected drug overdose, consult the regional poison control center.

Overdosage may cause persistent diuresis, excessive peripheral vasodilatation (with marked hypotension, electrolyte disturbances, cardiac arrhythmias, impairment of consciousness up to and including coma and cerebral convulsions).

Management
Treatment is symptomatic and supportive. Primary detoxification by, for example, administration of adsorbants may be considered. In the event of hypotension, administration of a $_1$-adrenergic agonists (e.g. norepinephrine, dopamine) or angiotensin II (angiotensinamide), must be considered in addition to volume and salt substitution.

In attempting to eliminate ramipril, or ramiprilat, limited/no experience is available concerning the efficacy of forced diuresis, altering urine pH, haemofiltration or dialysis. If dialysis or haemofiltration is nevertheless contemplated, consider risks of anaphylactoid reactions with high flux membrane (see WARNINGS AND PRECAUTIONS, Immune, Anaphylactoid reactions to ACE inhibtors).

Removal of thiazide diuretics by dialysis is negligible.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Ramipril and hydrochlorothiazide (tablets) (ramipril/hydrochlorothiazide) has antihypertensive and diuretic effects. Ramipril and hydrochlorothiazide are used singly or together for antihypertensive

therapy. The antihypertensive effects of both substances are complementary.
The blood-pressure-lowering effects of both components together are greater than the effect of either monotherapy. In patients treated with ramipril and a thiazide diuretic there was essentially no change in serum potassium (see WARNINGS AND PRECAUTIONS, Metabolism).

Pharmacodynamics

Ramipril: Administration of ramipril causes a marked reduction in peripheral arterial resistance. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.

In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.

Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Hydrochlorothiazide: Electrolyte and water excretion starts approximately 2 hours after administration, reaches its peak after 3 to 6 hours and lasts from 6 to 12 hours.

The onset of the antihypertensive effect requires several days and administration for 2 to 4 weeks is necessary for optimal therapeutic effect.

Pharmacokinetics

Table 3: Summary of pharmacokinetic parameters after single doses of 5/25 mg ALTACE® HCT, 5 mg ramipril, 25 mg HCT or 5 mg ramipril + 25 mg HCT from study HOE9829/1502				
Arithmetic Mean (CV%) (Geometric LS Mean)				
Substrate	C_{max} [ng/mL]	t_{max} [h]	AUC_T [ng*h/mL]	$AUC_{(0-72)}$ [ng*h/mL]
ALTACE® HCT 5/25 mg tablet				
- ramipril	19.348±37.7 (17.896)	0.50±26.8	25.256±63.3 (21.646)	---
- ramiprilat	6.576±47.4 (6.061)	2.50±33.3	---	119.102±25.3 (116.192)
- HCT	140.95±23.8 (137.08)	2.00±44.2	993.53±18.5 (980.65)	---
Ramipril 5 mg tablet				
- ramipril	21.712±42.2 (19.649)	0.50±70.0	26.546±70.9 (22.500)	---
- ramiprilat	6.588±62.7 (5.703)	2.57±51.3	---	116.693±29.0 (110.362)
HCT 25 mg tablet:				
- HCT	140.52±24.2 (136.21)	2.00±47.3	1048.70±24.8 (1021.52)	---
5 mg ramipril tablet + 25 mg HCT tablet				
- ramipril	21.035±33.1 (19.896)	0.53±35.3	25.317±65.1 (22.024)	---
- ramiprilat	5.941 ± 51.6 (5.328)	3.00±38.0	---	108.716±21.1 (105.633)
- HCT	144.85±30.3 (138.38)	2.00±36.5	969.92±21.5 (953.41)	---

No significant pharmacokinetic interaction has been observed between ramipril and hydrochlorothiazide administered as a fixed combination formulation of ramipril/hydrochlorothiazide tablets (ramipril/hydrochlorothiazide 5 mg/ 25 mg tablet Aventis Pharma Canada Inc.) under fasting conditions, on the basis of ramipril and hydrochlorothiazide parameters (C_{max} and AUC).

Ramipril

Absorption: ramipril is rapidly absorbed after oral administration. As measured by the recovery of radioactivity in the urine, which represents only one of the elimination routes, absorption of ramipril is at least 56%. Administration of ramipril at the same time as food has no relevant effect on absorption.

Distribution: as a result of this activation/metabolization of the prodrug, approximately 20% of orally administered ramipril is bioavailable.

The bioavailability of ramiprilat after oral administration of 2.5 and 5 mg ramipril is approximately 45% compared with its availability after intravenous administration of the same doses.

Peak plasma concentrations of ramipril are reached within 1 hour after oral administration. Peak plasma concentrations of ramiprilat are reached 2 to 4 hours after oral administration of ramipril.

The protein-binding of ramipril and ramiprilat is approximately 73% and approximately 56% respectively.

Metabolism: the prodrug ramipril undergoes an extensive hepatic first pass metabolism, which is essential for the formation of the sole active metabolite ramiprilat (hydrolysis, which occurs principally in the liver). In addition to this activation into ramiprilat, ramipril is glucuronized and transformed into ramipril diketopiperazine (ester). Ramiprilat is glucuronized as well and transformed into ramiprilat diketopiperazine (acid).

When high doses (10 mg) of ramipril are administered, impairment of hepatic function retards the activation of ramipril into ramiprilat, resulting in increased ramipril plasma levels.

Excretion: following oral administration of 10 mg of radioactive labelled ramipril, approximately 40% of total radioactivity is excreted in faeces and approximately 60% in urine. The elimination half-life of ramipril is approximately 1 hour.

Approximately 80 to 90% of the metabolites in urine and bile have been identified as ramiprilat or ramiprilat metabolites. Ramipril glucuronide and ramipril diketopiperazine represented approximately 10 to 20% of the total amount, whereas unmetabolized ramipril accounted for approximately 2%.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The initial distribution and elimination phase has a half-life of approximately 3 hours. It is followed by an intermediate phase (half-life approximately 15 hours) and a terminal phase with very low plasma ramiprilat concentrations and a half-life of approximately 4 to 5 days.

Despite this long terminal phase, a single daily dose of 2.5 mg ramipril or more yields steady state plasma concentrations of ramiprilat after approximately 4 days. The "effective" half-life, which is relevant for dosage, is 13 to 17 hours under multiple-dose conditions.

Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal

ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in persons with normal renal function (see WARNINGS AND PRECAUTIONS, Renal)

Hydrochlorothiazide

Absorption: approximately 70% of hydrochlorothiazide is absorbed after oral administration; the bioavailability of hydrochlorothiazide after oral administration is approximately 70%.

Distribution: approximately 40% of hydrochlorothiazide is bound to plasma proteins.

Metabolism: hydrochlorothiazide undergo negligible hepatic metabolism and have not been shown to induce or inhibit any CYP450 isoenzymes.

Excretion: hydrochlorothiazide is excreted almost entirely (more than 95%) by renal route in unchanged form. After oral administration of a single dose, 50 to 70% is excreted within 24 hours.

The elimination half-life is 5 to 6 hours. In renal insufficiency excretion is reduced and the half-life prolonged. Renal clearance of hydrochlorothiazide correlates closely with creatinine clearance.

Special Populations and Conditions

Pediatrics
No data available.

Geriatrics
In healthy subjects aged between 65 and 76 years ramipril and ramiprilat kinetics are similar to those in healthy young subjects.

Gender
No data available.

Race
The average response to ACE inhibitor monotherapy was lower in black hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Cardiovascular Insufficiency
The clearance of hydrochlorothiazide may be decreased in patients with congestive heart failure.

Nursing Women
Hydrochlorothiazide passes into breast milk in small quantities.
Studies in lactating animals have shown that ramipril passes into the milk.
(WARNINGS AND PRECAUTIONS, Breastfeeding)

Hepatic Insufficiency
No relevant changes in the pharmacokinetics of hydrochlorothiazide have been noted in liver

cirrhosis.

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.

Hepatic metabolism does not play a significant role in the elimination of hydrochlorothiazide.

Hydrochlorothiazide should not be administered in hepatic coma or pre-coma. It should be used only with caution in patients with progressive hepatic disease (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary).

Renal Insufficiency
Renal excretion of ramipril, ramiprilat, and its metabolite is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decreases more slowly than in persons with normal renal function.

In patients with creatinine clearance less than 40 mL/min/1.73m^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, Dosage in patients with impaired renal function)

The clearance of hydrochlorothiazide is decreased in renal failure.

Hydrochlorothiazide must be present at the site of action in the renal tubule in sufficient concentration in order to achieve its therapeutic effect. Hydrochlorothiazide reaches its site of action almost exclusively by secretion into the tubular fluid via the organic acid cotransporter. In mild renal insufficiency, higher doses are required to achieve sufficient concentrations of drug at the site of action due to decreased tubular secretion in renal failure. However, hydrochlorothiazide becomes ineffective once creatinine clearance drops below 30 to 50 mL/min.

Genetic Polymorphism
No information available.

STORAGE AND STABILITY

Store RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) in original container at room temperature, between 15°C - 25°C and not beyond the date indicated on the container. Protect from heat and humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) **5 mg/12.5 mg tablets** are pink, oblong, scored tablet with “RH” and “2A” debossed on either side of the score on one side and nothing on the

other scored side. Each tablet contains 5 mg of Ramipril, 12.5 mg of Hydrochlorothiazide and the following non medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone (XL), Hypromellose, Microcrystalline cellulose (Vivapur 12), Lactose Monohydrate, Sodium Stearyl Fumarate, Red iron oxide.

RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) **10 mg/12.5 mg tablets** are orange, oblong, scored tablet with "RH" and "3A" debossed on either side of the score on one side and nothing on the other scored side. Each tablet contains 10 mg of Ramipril, 12.5 mg of Hydrochlorothiazide and the following non medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone (XL), Hypromellose, iron Oxide IC07434 (Yellow #10) Microcrystalline cellulose (Vivapur 12), Lactose Monohydrate, Sodium Stearyl Fumarate and Red iron oxide.

RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) **10 mg/25 mg tablets** are pink, oblong, scored tablet with "RH" and "3V" debossed on either side of the score on one side and nothing on the other scored side. Each tablet contains 10 mg of Ramipril, 25 mg of Hydrochlorothiazide and the following non medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone (XL), Hypromellose, Microcrystalline cellulose (Vivapur 12), Lactose Monohydrate, Sodium Stearyl Fumarate, Red iron oxide.

RAMIPRIL-HCTZ 5 mg/12.5 mg, 10 mg/12.5 mg, and 10 mg/25 mg tablets are supplied in bottle of 100 tablets and blister of 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ramipril

Chemical name:

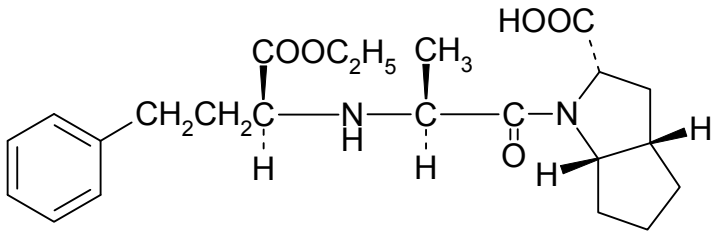
Company's Chemical name: 2-[N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-(1 S,3S,5S)-2-azabicyclo-[3.3.0]octane-3-carboxylic acid

USP Chemical name:Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, [2S-[1 *[R*(R*)],2a* ,3a^{ß},6a^{ß}]]-.(2S,3aS,6aS)-1-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl] alanyl] octahydrocyclopenta [b]pyrrole-2 -carboxylic acid, 1-ethyl ester

Molecular formula and molecular mass: $C_{23}H_{32}N_20_5$

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.

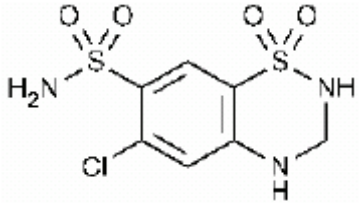
Proper name: Hydrochlorothiazide

Chemical name: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Molecular formula and molecular mass: $C_7H_8C1N_30_4S_2$

Molecular mass: 297.74

Structural formula:



Physicochemical properties: A white crystalline powder, very slightly soluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

CLINICAL TRIALS

Study demographics and trial design

Table 4 - Summary of patient demographics for clinical trials in specific indication

Study No.	Trial design	Dosage, route of administration and duration (number of weeks)	Study subjects (entered/completed)	Mean age (Range)	Gender (M/F)
HOE9829 /8/F/301/ HT (Study 7)	Multicentre, double-blind, randomized, placebo run-in phase	R: 2.5 mg/od tablets; H: 12.5 mg/od tablets; R+H (fixed comb): 2.5/12.5 mg/od Oral 12 weeks	R: 218/218; H: 220/220; R+H: 222/222	(20-75)	329/331
HOE498/ 2/MN/20 1/HT (Study 1)	Randomized, placebo-controlled, double-blind, with single-blind placebo run-in phase	P: — R: 2.5, 5.0, or 10.0 mg/od; H: 12.5, or 25.0 mg/od; R+H: 2.5+12.5, 2.5+25.0, 5.0+25.0, 10.0+12.5, or 10.0+25.0 mg/od Oral 6 weeks	P: 44/42 R: 136/134 H: 88/85 R+H: 266/257	48.2 (21-68)	302/232
HOE498-2 MN-302 HT (Study 5)	Multicentre, double-blind, randomized, parallel, placebo run-in phase	R: 10 mg od; H: 50 mg od; R+H: 10/50 mg od Oral 16 weeks	R: 93/75 non-responders: 35 H: 99/78 non-responders: 49	56 (29-80)	99/93
HOE498/ 8/USA/35 1/HT (Study 2)	Double-blind, stratified, randomized, with 3 parallel treatment groups, placebo wash-out period	R: 5 mg/od; H: 25 mg/od; R+H: 5/25 mg/od Oral 12 weeks	R: 120/111 H: 120/114 R+H: 120/113	(27-80)	238/122

R = Ramipril, H = Hydrochlorothiazide, od = once daily, bid = twice daily

Table 4 (Continued) - Summary of patient demographics for clinical trials in specific indication

Study No.	Trial design	Dosage, route of administration and duration (number of weeks)	Study subjects (entered/completed)	Mean age (Range)	Gender (M/F)
HOE498/ 2/MN/30 9/HT (Study 3)	Double-blind, multicentre. The study comprised of a 2 week placebo run-in phase	R: 5, or 10 mg/od; R+H: 5/25 mg/od Oral 10 weeks	Double-blind phase: Non-responders 5 R: 54/53 10 R: 53/50 R+H: 58/58 Responders 5 R: 59/58	57.0 (23-78)	119/121
HOE9829 /2/D/201/ HT (Study 6)	Open-label, uncontrolled, multicentre, one-year extension of HOE498/2/M N/309/HT (Study 3)	R+H (fixed comb): 5/25 or 10/50 mg/od tablet oral 52 weeks	R+H (5/25mg): 73/68; R+H (10/50mg): 3/3; R+H (5/25mg or 10/50 mg): 9/9	(26-74)	55/41
HOE498/ 2/MN/31 0/HT (Study 4)	Open-label, uncontrolled, multicentre, one-year extension of HOE498/2/M N/309/HT (Study 3)	Responders: R: 5 mg/od Nonresponders: R+H: 5+25 mg/od Oral 12 months	R: 38/31 R+H <50 weeks: 38/32 R+H >50 weeks: 83/81	(25-78)	86/73

R = Ramipril, H = Hydrochlorothiazide, od = once daily, bid = twice daily

All populations included in the 7 phase II/III safety studies were similar, male and female patients suffering from mild to moderate hypertension (WHO stage I or II hypertension).

A subgroup analysis was performed with data derived from studies 1, 2, 3, and 4 in order to assess the efficacy and/or safety of the combination of ramipril/hydrochlorothiazide in different risk groups. The different risk groups analysed in the Subgroup Analyses included elderly, diabetic, renally insufficient, and patients with concomitant medications (non-steroidal anti-inflammatory drugs, nitrates, digitalis, and antigout agents). A total of 1180 patients participated in studies 1 to 4.

Study Results

Table 5- Results of All Efficacy Studies for Ramipril/HCT in Reducing Blood Pressure in Essential Hypertension

Study	Treatment Arm	# Enrolled/ Completed	Supine mean systolic and diastolic BP [Systolic/Diastolic (mm Hg)]					Primary Endpoint	Other Comments
			Baseline	Endpoint (Each study varies in duration, so values are only inserted where applicable.)					
				6 wks	8 wks	10 wks	12 wks		
HOE9829 – 301HT (Study 7)	R: 2.5 mg	218/185	166.7/102.2		149.3/89.1			Supine diastolic blood pressure – level of response.	The data represents the per-protocol analysis. The difference between R+H and H alone was not significant but were significant in the intent-to-treat analysis.
	H: 12.5 mg	220/183	167.9/102.9		149.3/90.4				
	R+H: 2.5/12.5 mg	222/167	167.5/102.1		147.4/87.8				

R= Ramipril
H= Hydrochlorothiazide (HCT)

Table 5 (Continued)- Results of All Efficacy Studies for Ramipril/HCT in Reducing Blood Pressure in Essential Hypertension

Study	Treatment Arm	# Enrolled/ Completed	Supine mean systolic and diastolic BP [Systolic/Diastolic (mm Hg)]					Primary Endpoint	Other Comments
			Baseline	Endpoint (Each study varies in duration, so values are only inserted where applicable.)					
				6 wks	8 wks	10 wks	12 wks		
HOE498 – 201HT (Study 1)	R: 2.5 mg	44/44	162.5/106.4	153.3/99.7				Change in supine and standing diastolic and systolic blood pressure.	The combinations (5/12.5 mg, 5/25 mg and 10/12.5 mg) produced significantly greater blood pressure reductions than their respective components at week 6 and endpoint.
	R: 5 mg	48/47	161.0/106.0	149.1/100.0					
	R: 10 mg	44/43	157.4/107.1	146.2/98.6					
	H: 12.5 mg	46/45	161.3/107.2	152.6/100.7					
	H: 25 mg	42/40	161.0/106.6	149.1/98.2					
	R+H: 2.5/12.5 mg	45/42	160.1/106.1	145.0/97.2					
	R+H: 2.5/25 mg	43/42	163.0/105.9	147.1/97.2					
	R+H: 5/12.5 mg	44/44	161.8/106.8	144.0/95.9					
	R+H: 5/25 mg	47/44	163.8/108.1	143.4/94.7					
	R+H: 10/12.5 mg	43/43	158.7/106.6	141.1/93.6					
	R+H: 10/25 mg	44/42	163.9/106.4	142.9/95.1					

R= Ramipril
H= Hydrochlorothiazide (HCT)

Table 5 (Continued)- Results of All Efficacy Studies for Ramipril/HCT in Reducing Blood Pressure in Essential Hypertension

Study	Treatment Arm	# Enrolled/ Completed	Supine mean systolic and diastolic BP [Systolic/Diastolic (mm Hg)]				Primary Endpoint	Other Comments
			Baseline	Endpoint (Each study varies in duration, so values are only inserted where applicable.)				
				6 wks	8 wks	10 wks	12 wks	
HOE498 – 302HT (Study 5)	Responders:		Phase 1:					The results are for the second phase (weeks 11 – 16), except for the baseline blood pressure values. In the second phase, responders continued with monotherapy and non-responders were placed on combination therapy.
	R: 10 mg	30	166.4/102.8	148.7/84.7			148.8/84.5	
	H: 50 mg	45	167.6/101.9 (N=129)	143.5/84.8			139.4/83.2	
	Non-responders:							
	R+H: 10/50 mg	84		160.4/99.1			149.5/90.85	
HOE498 – 351HT (Study 2)	R: 5 mg	120/111	157.3/104.4	152.2/98.1				Subjects are stratified according to race (blacks/non-blacks). R+H was equally effective in both blacks and non-blacks in decreasing diastolic and systolic blood pressure.
	H: 25 mg	120/114	159.7/104.2	145.4/93.9				
	R+H: 5/25 mg	120/113	158.1/104.4	141.8/91.9				

Change in systolic and diastolic supine and standing blood pressure.

Change in systolic and diastolic supine and standing blood pressure.

R= Ramipril
H= Hydrochlorothiazide (HCT)

Table 5 (Continued)- Results of All Efficacy Studies for Ramipril/HCT in Reducing Blood Pressure in Essential Hypertension

Study	Treatment Arm	# Enrolled/ Completed	Supine mean systolic and diastolic BP [Systolic/Diastolic (mm Hg)]					Primary Endpoint	Other Comments
			Baseline	Endpoint (Each study varies in duration, so values are only inserted where applicable.)					
				6 wks	8 wks	10 wks	12 wks		
HOE498 – 309 HT (Study 3)	Responders: R: 5 mg	59/58	170.7/100.9			146.6/86.5		Change in systolic and diastolic supine and standing blood pressure.	The results are for the 2nd phase of the study. Responders continued with monotherapy and non-responders were kept on monotherapy or placed on combination therapy.
	Non-Responders: R: 5 mg	54/53	171.5/103.2			152.8/90.6			
	R: 10 mg	53/50	174.2/102.7			152.1/89.6			
	R+H: 5/25 mg	58/57	176.0/102.5			149.0/87.0			
HOE9829 – 201HT (Study 6)	R+H: 5/25 mg	73/73	Not available, since this is a one-year extension.					Change in systolic and diastolic supine and standing blood pressure.	There was no evidence of an increase in mean blood pressure or of an increase in the number of nonresponders during long-term treatment.
	R+H: 10/50 mg	3/3							
	SWITCH (R+H): 5/25 or 10/50 mg	9/9							

R= Ramipril
H= Hydrochlorothiazide (HCT)

Table 5 (Continued)- Results of All Efficacy Studies for Ramipril/HCT in Reducing Blood Pressure in Essential Hypertension

Study	Treatment Arm	# Enrolled/ Completed	Supine mean systolic and diastolic BP [Systolic/Diastolic (mm Hg)]				Primary Endpoint	Other Comments
			Baseline	Endpoint (Each study varies in duration, so values are only inserted where applicable.)				
				6 wks	8 wks	10 wks	12 wks	
HOE498 – 310HT (Study 4)	R: 5 mg	38/31					Change in systolic and diastolic supine and standing blood pressure.	There was no evidence of an increase in mean blood pressure or an increase in the number of non-responders during long-term treatment.
	R+H: 5/25 mg	83/81						
	SWITCH (R or R+H): 5 mg or 5/25 mg	38/32						

R= Ramipril
H= Hydrochlorothiazide (HCT)

Comparative Bioavailability Studies

In a 3-way crossover, comparative bioavailability study, two new strengths of combination ramipril/ hydrochlorothiazide, containing 10 mg ramipril with either 12.5 or 25 mg of hydrochlorothiazide, were found to be bioequivalent with Canadian references of ramipril 10 mg and hydrochlorothiazide 25 mg given concomitantly. Thirty-three healthy men between 18 and 45 years old were enrolled and randomized and thirty-one (31) subjects completed the study according to the protocol.

Table 6: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR RAMIPRIL (Test-1: 10/25 mg ramipril/HCT)

Ramipril (1 x 10 mg) **Measured Data** Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test-1** (1 x Ramipril 10 mg /HCT 25 mg)	**Reference** (1x Delix®protect 10 mg tablet + 1x Apo-Hydro 25 mg tablet)	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T (ng·h/mL)	42.387 48.797 (58.9)	40.469 52.003 (99.9)	104.74	96.53-113.65
AUC_∞ (ng·h/mL)	43.195 49.568 (58.3)	41.225 52.716 (98.7)	104.78	96.61-113.64
C_{max} (ng/mL)	30.860 33.457 (40.6)	31.667 35.216 (45.3)	97.45	86.24-110.12
T_{max}* (h)	0.50 (0.33-1.00)	0.50 (0.33-1.50)		
$T_{½}$# (h)	2.50 (34.0)	2.49 (35.8)		

HCT: Hydrochlorothiazide
*: Expressed as the median (range) only
#: Expressed as the arithmetic mean (%CV) only
Test-1: One fixed combination tablet containing ramipril 10 mg and hydrochlorothiazide 25 mg
Reference: One Delix®protect 10 mg tablet containing ramipril 10 mg (sanofi-aventis, Italy) and one Apo-Hydro 25 mg tablet (Apotex Inc., Canada) containing hydrochlorothiazide 25 mg.

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Table 7: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR HYDROCHLOROTHIAZIDE (Test-1: 10/25 mg ramipril/HCT)

Hydrochlorothiazide (1 x 25 mg) **Measured Data** Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test-1** (1 x Ramipril 10 mg /HCT 25 mg)	**Reference** (1x Delix®protect 10 mg tablet + 1x Apo-Hydro 25 mg tablet)	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T (ng·h/mL)	850.39 867.16 (21.0)	830.15 851.19 (22.6)	102.44	97.84-107.26
AUC_∞ (ng·h/mL)	892.13 908.38 (20.3)	882.89 902.61 (21.3)	101.05	96.94-105.32
C_{max} (ng/mL)	121.11 125.58 (26.7)	109.18 114.68 (32.0)	110.93	102.26-120.33
T_{max} * (h)	2.00 (1.00-4.00)	2.00 (0.67-6.00)		
$T_{½}$ # (h)	9.79 (17.5)	9.71 (22.2)		

HCT: Hydrochlorothiazide

* : Expressed as the median (range) only

: Expressed as the arithmetic mean (%CV) only

Test-1: One fixed combination tablet containing ramipril 10 mg and hydrochlorothiazide 25 mg.

Reference: One Delix®protect 10 mg tablet (sanofi-aventis, Italy) containing ramipril 10 mg and one Apo-Hydro 25 mg tablet (Apotex Inc., Canada) containing hydrochlorothiazide 25 mg.

Table 8: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR RAMIPRIL (Test-2: 10/12.5 mg ramipril/HCT)

Ramipril (1 x 10 mg) **Measured Data** Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test-2** (1 x Ramipril 10 mg /HCT 12.5 mg)	**Reference** (1x Delix®protect 10 mg tablet + 1x Apo-Hydro 25 mg tablet)	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T (ng·h/mL)	42.251 51.167 (73.1)	40.469 52.003 (99.9)	104.40	96.22-113.28
AUC_∞ (ng·h/mL)	42.998 51.831 (72.2)	41.225 52.716 (98.7)	104.30	96.17-113.12
C_{max} (ng/mL)	31.672 36.986 (59.7)	31.667 35.216 (45.3)	100.01	88.51-113.01
T_{max} * (h)	0.50 (0.33-1.50)	0.50 (0.33-1.50)		
$T_{½}$ # (h)	2.51 (31.2)	2.49 (35.8)		

HCT: Hydrochlorothiazide

* : Expressed as the median (range) only

: Expressed as the arithmetic mean (%CV) only

Test-2: One fixed combination tablet containing ramipril 10 mg and hydrochlorothiazide 12.5 mg. Hydrochlorothiazide is dose normalized to 25 mg.

Reference: One Delix®protect 10 mg tablet (sanofi-aventis, Italy) containing ramipril 10 mg and one Apo-Hydro 25 mg tablet (Apotex Inc., Canada) containing hydrochlorothiazide 25 mg.

Table 9: SUMMARY OF THE COMPARATIVE BIOAVAILABILITY DATA FOR HYDROCHLOROTHIAZIDE (Test-2: 10/12.5 mg ramipril/HCT)

Hydrochlorothiazide (1 x 25 mg) Measured Data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test-2** (1 x Ramipril 10 mg /HCT 12.5 mg)	**Reference** (1x Delix®protect 10 mg tablet + 1x Apo-Hydro 25 mg tablet)	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T (ng·h/mL)	764.89 783.93 (22.2)	830.15 851.19 (22.6)	92.14	88.00-96.47
AUC_∞ (ng·h/mL)	857.48 874.83 (20.3)	882.89 902.61 (21.3)	97.12	93.18-101.23
C_{max} (ng/mL)	112.43 116.29 (25.4)	109.18 114.68 (32.0)	102.98	94.94-111.71
T_{max} * (h)	2.00 (1.50-4.00)	2.00 (0.67-6.00)		
$T_{½}$ # (h)	8.73 (23.6)	9.71 (22.2)		

HCT: Hydrochlorothiazide
*: Expressed as the median (range) only
#: Expressed as the arithmetic mean (%CV) only
Test-2: One fixed combination tablet containing ramipril 10 mg and hydrochlorothiazide 12.5 mg. Hydrochlorothiazide is dose normalized to 25 mg.
Reference: One Delix®protect 10 mg tablet (sanofi-aventis, Italy) containing ramipril 10 mg and one Apo-Hydro 25 mg tablet (Apotex Inc., Canada) containing hydrochlorothiazide 25 mg.

In addition, a drug interaction study was conducted demonstrating comparable bioavailability between the clinically proven 5 mg ramipril/25 mg hydrochlorothiazide combination tablet and the Canadian reference tablets of 5 mg ramipril and 25 mg hydrochlorothiazide, taken concomitantly.

These results demonstrate that the bioavailability of ramipril and hydrochlorothiazide (tablets) is comparable to the bioavailability of the Canadian reference ramipril and hydrochlorothiazide tablets, taken concomitantly.

Comparative Bioavailability Studies

A blind, randomized, two-way crossover bioequivalence study was performed in normal healthy male volunteers (n=24) under fasting conditions on Ramipril/Hydrochlorothiazide tablets using Pro Doc Ltée RAMIPRIL-HCTZ 10 mg/25 mg tablets (Lot # P-1742, manufactured on December 2007) versus the reference product, ALTACE® HCT 10 mg/25 mg Tablets (Lot # B402, expiring on January 2010), by Sanofi-Aventis Canada Inc. The pharmacokinetic data calculated for the RAMIPRIL-HCTZ 10 mg/25 mg tablets and ALTACE® HCT 10 mg/25 mg tablets formulation are tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

RAMIPRIL

Ramipril/Hydrochlorothiazide (1 x 10mg/25mg tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng·h/mL)	19.002 21.594 (60.3)	20.757 23.559 (55.8)	91.55	85.78-97.69
AUC_I (ng·h/mL)	20.727 24.051 (62.7)	22.918 26.340 (55.9)	90.44	82.62-99.00
C_{max} (ng/mL)	22.002 25.395 (57.4)	25.305 29.998 (60.6)	86.95	74.43-101.57
T_{max}§ (h)	0.50 (0.25 – 1.00)	0.50 (0.25 – 2.00)		
$T_{½}$€ (h)	1.81 (51.1)	2.15 (47.7)		

*Ramipril-HCTZ, Pro Doc Ltée, Laval, Canada

†Altace®HCT, Sanofi-Aventis Canada, Laval, Québec, Canada

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV%)

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

HYDROCHLOROTHIAZIDE

Ramipril/Hydrochlorothiazide (1 x 10mg/25mg tablet) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng·h/mL)	936.45 964.83 (21.3)	962.32 999.94 (26.5)	97.31	91.46-103.54
AUC_I (ng·h/mL)	1034.01 1061.91 (19.9)	1057.46 1092.35 (23.9)	97.78	93.10-102.70
C_{max} (ng/mL)	148.05 153.79 (26.1)	156.75 165.89 (36.9)	94.45	84.40-105.69
T_{max}§ (h)	1.50 (1.00 – 4.00)	1.50 (1.25 – 4.00)		
$T_{½}$€ (h)	10.14 (16.5)	9.99 (15.6)		

*Ramipril-HCTZ, Pro Doc Ltée, Laval, Canada

†Altace®HCT, Sanofi-Aventis Canada, Laval, Québec, Canada

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV%)

DETAILED PHARMACOLOGY

Refer to RAMIPRIL Product Monograph and Thiazide Diuretics Product Monograph for information.

TOXICOLOGY

Acute toxicity
Ramipril: As it has an LD_{50} in excess of 10,000 mg/kg body weight in mice and rats and above 1000 mg/kg body weight in beagle hounds, oral administration of ramipril has been found to be devoid of acute toxicity.

Ramipril + Hydrochlorothiazide: The oral LD_{50} in rats and mice is in excess of 10,000 mg/kg body weight, i.e., the combination ramipril + hydrochlorothiazide (1:5) is totally devoid of acute toxicity. This is consistent with the results of acute toxicity testing of the single components.

Chronic toxicity
Ramipril: Studies involving chronic administration have been conducted in rats, dogs and monkeys. In rats, daily doses of the order of 40 mg/kg body weight lead to shifts in plasma electrolytes and to anaemia. At daily doses of 3.2 mg/kg body weight or higher there was some evidence of changes in renal morphology (distal tubular atrophy). However, these effects can be explained in pharmacodynamic terms and are characteristic of the substance class. Daily doses of 2 mg/kg body weight have been tolerated by rats without toxic effects. Tubular atrophy is encountered in rats, but not in dogs and monkeys.

As an expression of the pharmacodynamic activity of ramipril (a sign of increased renin production as a reaction to reduced angiotensin II formation), pronounced enlargement of the juxtaglomerular apparatus has been noted in the dog and monkey - especially at daily doses of 250 mg/kg body weight or higher. Indications of plasma electrolyte shifts and changes in blood picture have also been found in the dog and monkey. Dogs and monkeys tolerated daily doses of 2.5 mg/kg body weight and 8 mg/kg body weight respectively without harmful effects.

Ramipril + Hydrochlorothiazide: With the exception of disturbances in electrolyte balance, studies conducted in rats and monkeys yielded no conspicuous findings.

Reproduction toxicology
Ramipril: Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties.

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

The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at doses of 50 mg/kg body weight or higher.

Ramipril + Hydrochlorothiazide:

Rats
In studies on embryotoxicity, the combination was administered to rats in daily doses of 1, 10, 150, 600 or 2400 mg/kg body weight during the sensitive phase of organogenesis.

Hydrochlorothiazide has been studied in a similar way alone at daily doses of 125, 500 or 2000 mg/kg body weight; these doses corresponded to the proportions of hydrochlorothiazide contained in the 3 highest doses of the combination.

The studies in rats showed that dams tolerated the combination administered at dose levels of 1 mg/kg and 10 mg/kg body weight without complications. Doses of 150 mg/kg body weight and above showed toxic effects on dams and led to reduced food intake and weight development. Heart and liver weights were reduced. Clinical symptoms of toxicity and deaths occurred at dose levels of 2400 mg/kg body weight.

At dose levels of 150 mg/kg body weight and above, urine excretion increased, and after 2400 mg/kg body weight kidney weights were slightly increased. These effects are attributable to the pharmacodynamic action of hydrochlorothiazide.

1 mg/kg body weight does not impair the development of the embryo. Doses of 10 mg/kg body weight and above led to a slight retardation in development of the fetus, which manifested itself in delayed skeletal ossification and, at dose levels of 150 mg/kg body weight and above, in reduced body weight and reduced body length. Placenta weight was also reduced.

Morphological investigations conducted in fetuses revealed increased occurrences of dilatation of the renal pelvis and the ureter as well as waved and thickened ribs at dose levels of 150 mg/kg body weight and above and, at levels of 600 mg/kg body weight and above, bent and shortened scapula and bones of the limbs.

The studies with hydrochlorothiazide alone confirm that the retardation of fetal growth is attributable to the diuretic. The other findings point to a joint effect of the two single components in the combination.

The study in rats revealed that the combination is somewhat more toxic than either of the single components, but without any signs of a teratogenic effect of the combination or of hydrochlorothiazide.

Other studies were conducted in rats to determine the peri- and postnatal toxicity of the combination; doses of 10 and 60 mg/kg body weight daily were given orally during the last third of pregnancy and during the 3 weeks of lactation. At doses of 10 mg/kg body weight, the drug neither had an adverse effect on the dams' general condition, the course of pregnancy or parturition, nor did it lead to a disturbance of intrauterine and postnatal development of the progeny.

After administration of 60 mg/kg body weight, the dams reduced food intake slightly, and the pups showed slightly reduced weights at birth and during the first week thereafter. In the subsequent period, the postnatal development of the pups turned up no conspicuous findings. The incidence of dilatation of the renal pelvis (such as has been noted following higher doses of ramipril) was not increased.

Rabbits
In studies on embryotoxicity, the combination was administered to rabbits in daily doses of 0.96, 2.40 or 6.00 mg/kg body weight during the sensitive phase of organogenesis.

A further group received hydrochlorothiazide (2 mg/kg; corresponding to the amount in the 2.40 mg/kg ramipril +hydrochlorothiazide dose group).

Administration of the combination in rabbits at dose levels of 0.96 mg/kg body weight led to a slight reduction in food intake and stagnation in body weight. However, it had no adverse effect on the intrauterine development in the progeny.

Following administration at dose levels of 2.40 and 6.00 mg/kg body weight, the dams reduced their intake of food and water and lost weight; furthermore, deaths and spontaneous abortions occurred at these dose levels and living fetuses showed slightly retarded growth at birth. No signs of external anomalies or of anomalies affecting internal organs and skeleton of the fetuses were detected which could be attributed to administration of the combination.

Hydrochlorothiazide alone administered at daily doses of 2 mg/kg body weight was tolerated by the dams and their fetuses.

From this study, it can be concluded that the combination is slightly more toxic for the damns than either component alone and that this combination did not provoke teratogenic changes.

Studies on possible impairment of fertility and reproductive capability were not conducted with the combination, since no toxic effect was to be expected on the basis of results in the single components.

Immunotoxicology
Ramipril: Toxicology studies have yielded no indication that ramipril possesses any immunotoxic effects.

Mutagenicity
Ramipril: Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.

Ramipril + **Hydrochlorothiazide:** Mutagenicity studies were not conducted with the combination since the results of tests with each component alone have shown no evidence of any such risk.

Carcinogenicity
Ramipril: Long-term studies in rat and mouse have yielded no indication of any tumorigenic effect. Renal tubules with oxyphilic cells and tubules with oxyphilic cellular hyperplasia in rats are regarded as response to functional alterations and morphological changes, and not as a neoplastic or pre-neoplastic response.

Ramipril + **Hydrochlorothiazide:** Carcinogenicity studies were not conducted with the combination since the results of tests with each component alone have shown no evidence of any such risk.

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PART III: CONSUMER INFORMATION

Pr RAMIPRIL-HCTZ
(ramipril and hydrochlorothiazide Tablets)

This leaflet is part III of a three-part "Product Monograph" published when RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RAMIPRIL-HCTZ. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for

RAMIPRIL-HCTZ was prescribed to you by your doctor to lower your blood pressure.

What it does
RAMIPRIL-HCTZ contains ramipril, which is one of a group of medicines called ACE (angiotensin converting enzyme) inhibitors which acts on the heart and blood vessel. Ramipril blocks an enzyme in the body that is necessary to produce a substance that causes blood vessels to tighten.

RAMIPRIL-HCTZ contains also hydrochlorothiazide which is one of a group of medicines called diuretics. Diuretics are sometimes called water pills. They lower the amount of salt and water in your body, which helps to lower your blood pressure.

When it should not be used

You must not take RAMIPRIL-HCTZ if:

- You have had an allergic reaction to ramipril, any other ACE inhibitor, hydrochlorothiazide, thiazide diuretics, any of the ingredients in this medicine or sulfonamide-derived drugs
- You have a history of angioedema (swelling around your face, throat or tongue)
- You are pregnant or breast feeding

What the medicinal ingredients are
RAMIPRIL-HCTZ contains ramipril and hydrochlorothiazide.

What the important nonmedicinal ingredients are
RAMIPRIL-HCTZ 5mg/12.5 mg, 10 mg/12.5mg, and 10 mg/25 mg tablets contain the following non medicinal ingredients: Colloidal Silicon Dioxide, Crospovidone (XL), Hypromellose, Microcrystalline cellulose (Vivapur 12), Lactose Monohydrate and Sodium Stearyl Fumarate. The 5 mg/12.5 mg and 10 mg/25 mg contain also Red Iron Oxide and the 10 mg/12.5 mg strength contain also Iron Oxide IC07434 (Yellow #10) and Red Iron Oxide.

What dosage forms it comes in
RAMIPRIL-HCTZ is available in tablets of the following strengths.

- 5 mg ramipril/12.5 mg hydrochlorothiazide
- 10 mg ramipril/12.5 mg hydrochlorothiazide
- 10 mg ramipril/25 mg hydrochlorothiazide

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions RAMIPRIL-HCTZ *should not be used during pregnancy. If you discover that you are pregnant while taking* RAMIPRIL-HCTZ*, stop the medication and please contact your physician.*

Have you told your doctor everything about your condition and of any problems you may have had with taking medicines in the past?

BEFORE you use RAMIPRIL-HCTZ talk to your doctor or pharmacist if:

- You have to perform tasks that require special attention (for example, operating a vehicle or machinery);
- You have heart problems or if you have any kidney or liver diseases
- You are on haemodialysis;
- You are allergic to RAMIPRIL-HCTZ or any of its ingredients;
- You have a history of angioedema (swelling around your face, throat or tongue);
- You have lupus erythematosus (disorders of the immune system) or scleroderma (disease that can cause thickening, hardening, or tightening of the skin, blood vessels and internal organs);
- **You are pregnant, breast-feeding or thinking of becoming pregnant**

Taking RAMIPRIL-HCTZ during pregnancy can cause injury and even death to the foetus. This medicine should not be used during pregnancy. If you become pregnant while taking RAMIPRIL-HCTZ, stop the medication and report promptly to your doctor. It is not known if RAMIPRIL-HCTZ passes into breast milk. You should not breast-feed while taking RAMIPRIL-HCTZ.

INTERACTIONS WITH THIS MEDICATION

Some drugs may have negative effect on RAMIPRIL-HCTZ, or RAMIPRIL-HCTZ may have negative effect on other drugs. If you are currently taking a medication, whether on prescription or otherwise, inform your doctor or pharmacist.

Drugs that may interact with RAMIPRIL-HCTZ include:

- Diuretics (water pills), potassium retaining diuretics;
- Medicines for high blood pressure, heart disease;
- Lithium salts;
- Antidiabetic agents
- Digitalis preparation (Digoxin)
- Non steroidal anti-inflammatory drugs
- Corticosteroids;
- Sympathomimetics which may be found in some decongestants, cough/cold medicines;
- Anaesthetics.

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.

PROPER USE OF THIS MEDICATION

It is important to take RAMIPRIL-HCTZ at the same time every day as prescribed by your doctor. Generally, it is recommended that the daily dose be administered in the morning.

Swallow your tablet whole with sufficient amount of water (approximately half a glass), before, during or after meal. Do not chew or crush the tablets.

Usual dose

Your starting dose will be determined by your doctor taking into account pre-existing blood pressure treatment. The maximum daily dose of RAMIPRIL-HCTZ is 10 mg/50 mg.

Overdose

In case of overdosage, contact your doctor, nearest hospital emergency department or regional poison control center."

Missed Dose

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, RAMIPRIL-HCTZ may cause side effects. After you have started taking RAMIPRIL-HCTZ, it is important that you tell your doctor at once about any unexplained symptom you might experience. Examples of occasional side effects include:

- Dizziness
- Headache
- Flu-like symptoms such as sore throat, fever, malaise, muscle pain, rash, nausea, vomiting, diarrhea
- Dry cough, mouth ulcer, tongue pain
- Chest pain
- Unusual tiredness and/or weakness
- Palpitations and tachycardia
- Mood changes, nervousness, restlessness, confusion
- Problems with sleeping
- Sexual difficulties in men
- Very small number of people find that this medicine affects their sense of taste and smell.

If you feel ill after you have started taking RAMIPRIL-HCTZ tablets, or notice anything unusual or unexpected, tell your doctor or seek medical assistance.

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

	Symptom/ Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist*
		Only If Severe	In all cases	
Common	*Hypersensitivity Reactions* Skin rash, skin eruption or other effect on the skin or eyes, itching or fever			√
Uncommon	Abdominal pain		√	
	Hypotension Fainting when the Blood Pressure is Too low			√
	Allergic reactions Swelling of the lips, face or neck, accompanied by difficulty in breathing, speaking or swallowing (signs of angioedema). Intestinal angioedema may also occur and is characterized by abdominal pain (with or without nausea or vomiting)			√
	Liver disorder Symptoms include nausea, loss of appetite, vomiting combined with itching, upper abdominal pain, yellowing of the skin or eyes (sign of jaundice or hepatitis)			

*** If you think you have these side effects, it is important that you seek medical advice from your doctor immediately.**

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

HOW TO STORE IT

Store RAMIPRIL-HCTZ in original container at room temperature, between 15°C - 25°C and not beyond the date indicated on the container. Protect from heat and humidity.

Keep out of reach of children.

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

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
-Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web aite at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or info@prodoc.qc.ca.

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Last revised: November 6, 2013