PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]pms-RAMIPRIL-HCTZ

Ramipril and Hydrochlorothiazide Tablets

Tablets, 10/12.5 mg, 10/25 mg, Oral

Angiotensin Converting Enzyme Inhibitor Plus Diuretic

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RECENT MAJOR LABEL CHANGES

7 WARNING AND PRECAUTIONS, Ophthalmologic	10/2021
7 WARNING AND PRECAUTIONS, Respiratory	06/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

pms-RAMIPRIL-HCTZ is not indicated for initial therapy (see 4 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 pms-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.

Pediatrics
Pediatrics (< 18 years of age): The safety and effectiveness of ramipril and hydrochlorothiazide in pediatric patients have not been established. Therefore, pms-RAMIPRIL-HCTZ is not indicated in this patient population.

Geriatrics
Geriatrics (> 65 years of age): There is limited clinical experience with ramipril and hydrochlorothiazide in the elderly (> 65 years) (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug, any other angiotensin converting enzyme inhibitor (ACE inhibitor), other thiazide diuretics, sulfonamides or any ingredient in the formulation or component of the container. For a complete listing of ingredients, see 6 DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients who have a history of hereditary/idiopathic angioedema with or without treatment with an ACE inhibitor (see 7 WARNINGS AND PRECAUTIONS, Immune, Angioedema)
- Pregnant and nursing women (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).
- Patients with hemodynamically relevant bilateral renal artery stenosis, or unilateral in the single kidney (see 7 WARNINGS AND PRECAUTIONS, Renal, Renal impairment)
- Patients with hypotensive states or hemodynamically unstable states
- **Concomitant use with sacubitril/valsartan due to an increased risk of angioedema. Do not initiate pms-RAMIPRIL-HCTZ until at least 36 hours have elapsed following the last dose of sacubitril/valsartan. In the case of a switch from pms-RAMIPRIL-HCTZ to sacubitril/valsartan, do not start sacubitril/valsartan until at least 36 hours have elapsed following the last dose of pms-RAMIPRIL-HCTZ.**
- Combination with aliskiren-containing drugs in patients with:
  - diabetes mellitus (type 1 or type 2)

  - moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2)
  - hyperkalemia(> 5 mMol/L)
  - congestive heart failure who are hypotensive (see 7 WARNINGS ANDPRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS))
- Combination with angiotensin II receptor antagonists (ARBs) in patients with:
  - diabetes with end organ damage
  - moderate to severe kidney insufficiency (GFR< 60 mL/min/1.73m^2),
  - hyperkalemia(> 5mMol/L) or
  - congestive heart failure who are hypotensive (see 7 WARNINGS ANDPRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS))
- Combination with extracorporeal treatments leading to contact of blood with negatively charged surfaces since such use may lead to anaphylactoid reactions. Such extracorporeal treatments include dialysis or hemofiltration with certain high-flux (e.g., polyacrylonitril) membranes and low-density lipoprotein apheresis with dextran sulfate (see 7 WARNINGS AND PRECAUTIONS, Immune).
- Patients with anuria
- Patients with severe renal impairment (creatinine clearance <30 ml/min/1.73m^2)
- Patients on dialysis
- Patients with severe hepatic impairment
- Patients with clinically relevant electrolyte disturbances (e.g., hypokalemia, hyponatremia or hypercalcemia)

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus (see 7.1.1Pregnant Women). When pregnancy is detected, pms-RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) should be discontinued as soon as possible (see 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

Once the patient has been successfully titrated with the individual components as described below, pms-RAMIPRIL-HCTZ may be substituted if the titrated dose and dosing schedule can be achieved by the fixed combination (see 1 INDICATIONS, and 7 WARNINGS AND PRECAUTIONS).

Usual dosage: 2.5 mg ramipril and 12.5 mg hydrochlorothiazide daily. Generally, it is recommended that the daily dose be administered in the morning as a single dose.

Due to the risk of angioedema when used concomitantly with sacubitril/valsartan, pms-RAMIPRIL-HCTZ must not be started until 36 hours has passed following the last dose of sacubitril/valsartan (see 2 CONTRAINDICATIONS).

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

Maximum daily dose: 10 mg ramipril and 50 mg hydrochlorothiazide.

Dosage in elderly patients
Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients (see 7 WARNINGS AND PRECAUTIONS).

Dosage in patients with impaired renal function
Moderate renal impairment (creatinine clearance 30- 60 ml/min/1.73 m^2): In patients with moderate renal impairment, treatment is started with ramipril alone at a daily dose of 1.25 mg. After gradually increasing the dose of ramipril, medication with the combination preparation is started at a daily dose of 2.5 mg ramipril /12.5 mg hydrochlorothiazide (not available from Pharmascience Inc.). Maximum permitted daily dose: 5 mg ramipril/ 25 mg hydrochlorothiazide (not available from Pharmascience Inc.). pms-RAMIPRIL-HCTZ 10 mg/12.5 mg and pms-RAMIPRIL-HCTZ 10 mg/25 mg MUST NOT be used in these patients.

pms-RAMIPRIL-HCTZ is contraindicated in patients with severe renal impairment (creatinine clearance<30 ml/min/1.73 m^2) and in dialysis patients (see 2 CONTRAINDICATIONS).

Dosage in patients with impaired hepatic function
Mild or moderate hepatic impairment: In patients with mild to moderate hepatic impairment, treatment with pms-RAMIPRIL-HCTZ must be initiated only under close medical supervision and the maximum daily dose is 2.5 mg of ramipril/12.5 mg hydrochlorothiazide (not available from Pharmascience Inc.). pms-RAMIPRIL-HCTZ 10 mg/12.5 mg and 10 mg/25 mg MUST NOT be used in these patients.

pms-RAMIPRIL-HCTZ is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS).

Dosing in patients pre-treated with diuretics
In patients pre-treated with a diuretic, consideration must be given to discontinuing the diuretic≥2- 3 days (depending on the duration of action of the diuretic) before starting treatment with pms-RAMIPRIL-HCTZ or at least to reducing the diuretic dose. Should discontinuation not be possible, it is recommended that treatment be initiated with the smallest possible dosage of ramipril (1.25 mg daily) in a free combination. It is recommended that, subsequently, a changeover be made to an initial daily dose of ≤2.5 mg ramipril /12.5 mg hydrochlorothiazide (not available from Pharmascience Inc.).

4.4 Administration

pms-RAMIPRIL-HCTZ tablets should be swallowed with sufficient amounts of liquid (approximately ½ 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 effect is to be expected with pms-RAMIPRIL-HCTZ.

4.5 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.

5 OVERDOSAGE

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), bradycardia, renal failure, paresis and paralytic ileus.

In patients with obstruction of urinary outflow (e.g., from prostatic hyperplasia), sudden diuresis may induce acute urinary retention with overdistension of the bladder.

Management
Treatment is symptomatic and supportive. Primary detoxification by, for example, administration of adsorbants may be considered. In the event of hypotension, administration of α_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, there is limited/no experience available concerning the efficacy of forced diuresis, altering urine pH, hemofiltration or dialysis. If dialysis or hemofiltration is nevertheless contemplated, consider risks of anaphylactoid reactions with high flux membrane (see 7 WARNINGS AND PRECAUTIONS, Immune, Anaphylactoid Reactions to ACE Inhibitors during membrane exposure).

Removal of thiazide diuretics by dialysis is negligible.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet, 10 mg ramipril/12.5 mg hydrochlorothiazide	Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Lactose Monohydrate, Microcrystalline Cellulose, Red Iron Oxide, Sodium Stearyl Fumarateand Yellow Iron Oxide.
Oral	Tablet, 10 mg ramipril/25 mg hydrochlorothiazide	Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Lactose Monohydrate, Microcrystalline Cellulose, Red Iron Oxide, Sodium Stearyl Fumarate.

Table 2: Tablet Description

pms-RAMIPRIL-HCTZ	Description
pms-RAMIPRIL-HCTZ 10/12.5 (10 mg ramipril/12.5 mg hydrochlorothiazide)	Each 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.
pms-RAMIPRIL-HCTZ 10/25 (10 mg ramipril/25 mg hydrochlorothiazide)	Each 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

Both pms-RAMIPRIL-HCTZ (10 mg /12.5 mg, 10 mg/ 25 mg) combination tablets are packaged in cartons of 30 tablets.

Both pms-RAMIPRIL-HCTZ (10 mg /12.5 mg, 10 mg/ 25 mg) combination tablets are also available in plastic bottles of 100 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

General

Cough
A dry, persistent cough, which usually disappears only after withdrawal or lowering the dose 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 8.2 Clinical Trial Adverse Reactions).

Dual blockade of the Renin-Angiotensin System (RAS)
There is evidence that co-administration of ACE inhibitors, such as the ramipril component in ramipril and hydrochlorothiazide tablets, or of ARBs with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2).

Therefore, the use of pms-RAMIPRIL-HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).

The use of pms-RAMIPRIL-HCTZ in combination with an ARB is contraindicated in patients with diabetic nephropathy (see 2 CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including the ramipril component of pms-RAMIPRIL-HCTZ, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia (see 9 DRUG INTERACTIONS).

Carcinogenicity and Mutagenicity

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use. The certainty of the evidence was assessed by Health Canada (see 8.5 Post Market Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16 TOXICOLOGY, Carcinogenicity – Hydrochlorothiazide).

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate protection (e.g., a

broad-spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g., light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see 8.5 Post Market Adverse Reactions).

Cardiovascular

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

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

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

In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure (BP) could result in a myocardial infarction or cerebrovascular accident (see 8.5 Post-Market Adverse Reactions, Cardiovascular). Because of the potential fall in BP in these patients, therapy with pms-RAMIPRIL-HCTZ should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of pms-RAMIPRIL-HCTZ is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once BP has increased after volume expansion in hypertensive patients. However, lower doses of pms-RAMIPRIL-HCTZ should be considered. In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of pms-RAMIPRIL-HCTZ (see 8.5 Post-Market Adverse Reactions, Cardiovascular).

pms-RAMIPRIL-HCTZ may lower the state of patient alertness and/or reactivity, particularly at the start of treatment. Patients should be cautioned to report light-headedness, especially during the first few days of pms-RAMIPRIL-HCTZ therapy. If actual syncope occurs, the patients should be told to discontinue the drug and consult with their physician.

Driving a vehicle or performing other hazardous tasks
Some adverse effects (e.g., some symptoms of a reduction in blood pressure such as light-headedness, dizziness, syncope) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g., operating a vehicle or machinery).

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 8.5 Post-Market Adverse Reactions). Current experience with the drug shows the incidence to be rare.

Hematological reactions to ACE inhibitors are more likely to occur in patients with impaired renal function and in those with concomitant collagen disease (e.g., lupus erythematosus or scleroderma) or in those treated with other drugs that may cause changes of the blood picture. Periodic monitoring of white blood cell counts should be considered (see 7 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 8.5 Post-Market Adverse Reactions).

Hepatic/Biliary

Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre -existing liver abnormalities (see 8.5 Post-Market Adverse Reactions). In most cases the changes were reversed on discontinuation of the drug. Should the patient receiving pms-RAMIPRIL-HCTZ 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 pms-RAMIPRIL-HCTZ should be considered when appropriate.

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 8.5 Post-Market Adverse Reactions).

Thiazides should be used with caution in patients with mild to moderate impairment of hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. pms-RAMIPRIL-HCTZ should not be used in patients with severe impairment of hepatic function (see 2 CONTRAINDICATIONS).

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. In patients with impaired liver function, response to the treatment with ramipril may be either increased or reduced. In addition, in patients in whom severe liver cirrhosis with oedema and ascites is present, the RAS may be significantly activated. pms-RAMIPRIL-HCTZ should be used with particular caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Immune

Angioedema-Head and Neck

Angioedema has been reported in patients treated with ACE inhibitors including Ramipril. Life threatening angioedema has been reported in patients treated with ACE inhibitors including ramipril. The overall incidence is approximately 0.1 – 0.2%. Angioedema involving the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, pms-RAMIPRIL-HCTZ should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 - 0.5 ml of subcutaneous epinephrine solution 1:1000) should be administered promptly.

Angioedema, including laryngeal edema, may occur especially following the first dose of pms-RAMIPRIL-HCTZ. 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 pms-RAMIPRIL-HCTZ and consult with their physician.

An increased incidence of angioedema was observed in patients taking ACE inhibitors and mTOR inhibitors (mammalian target of rapamycin inhibitors) (see 9 DRUG INTERACTIONS).

Concomitant use of mTOR inhibitors, DPP-IV inhibitors and NEP inhibitors
Patients taking a concomitant mTOR inhibitor (e.g., sirolimus, everolimus, temsirolimus), DPP-IV inhibitor (e.g., sitagliptin) or neutral endopeptidase (NEP) inhibitor may be at increased risk for angioedema. Caution should be used when initiating ACE inhibitor therapy in patients already taking a mTOR, DPP-IV or NEP inhibitor or vice versa (see 9 DRUG INTERACTIONS).

Concomitant use of sacubitril/valsartan
A potential increased risk of angioedema has been reported with concomitant use of sacubitril/valsartan and ACE inhibitors (see 2 CONTRAINDICATIONS).

Angioedema – Intestinal
Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases, facial angioedema also occurred. The intestinal angioedema symptoms resolved after stopping the ACE inhibitor (see 8.5 Post-Market Adverse 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 2 CONTRAINDICATIONS).

Anaphylactoid Reactions to ACE Inhibitors during membrane exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes [e.g., polyacrylonitrile (PAN)] and treated concomitantly with an ACE inhibitor. Therefore, the use of pms-RAMIPRIL-HCTZ in patients dialyzed with high-flux membranes is contraindicated (see 2 CONTRAINDICATIONS). Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. If such treatment is required, a different type of dialysis membrane or a different class of antihypertensives is recommended.

Anaphylactoid Reactions to ACE Inhibitors during LDL apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding the ACE inhibitor therapy prior to each apheresis. Therefore, the use

of pms-RAMIPRIL-HCTZ in patients receiving low density lipoprotein apheresis with dextran sulfate is contraindicated (see 2 CONTRAINDICATIONS). If such treatment is required, consideration should be given to using a different type of apheresis or a different class of antihypertensive agents.

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

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.

Nitritoid Reactions – Gold
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ramipril and hydrochlorothiazide tablets (see 9 DRUG INTERACTIONS).

Metabolism

Thiazides, including hydrochlorothiazide, 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 9.4 Drug-Drug Interactions).

Elevated serum potassium (>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. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see 9.4 Drug-Drug Interactions, Agents increasing serum potassium).

Patients should be told not to use salt substitutes containing potassium, potassium supplements or potassium sparing diuretics without consulting their physician.

Monitoring and Laboratory Tests

Hematology monitoring
It is recommended that the white blood cell count be monitored to permit detection of a possible leukopenia due to the ACE inhibitor component of pms-RAMIPRIL-HCTZ, 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 7 WARNINGS AND PRECAUTIONS, Hematologic, Neutropenia/Agranulocytosis and; 9.4 Drug-Drug Interactions, Allopurinol, Immunosuppressants, Corticosteroids, Procainamide, Cytostatics and other substances that may change the blood picture).

Metabolism monitoring
Appropriate monitoring of electrolytes and blood sugar is required.
It is recommended that serum sodium, potassium, calcium, uric acid and blood glucose be monitored regularly. More frequent monitoring of serum potassium is necessary in patients with impaired renal function.

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

Particularly careful monitoring is required in patients with:

- heart failure
- renovascular disease (atherosclerotic renal artery stenosis (AS-RAS) and fibromuscular dysplasia(FMD))
- impairment of renal function
- kidney transplant
- elderly patients

Ophthalmologic

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.
The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

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

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

The use of ACE inhibitors – including the ramipril component of pms-RAMIPRIL-HCTZ – or ARBs with aliskiren-containing drugs is contraindicated in patients with diabetes mellitus (type 1 or 2),

moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2), hyperkalemia(> 5 mMol/L) or congestive heart failure who are hypotensive (see 2 CONTRAINDICATIONS and 9.5 Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin-System (RAS)).

Concomitant use of ACE inhibitors – including the ramipril component of pms-RAMIPRIL-HCTZ, with ARBs is contraindicated in patients with diabetes with end organ damage due to risk of hyperkalemia, moderate to severe kidney insufficiency (GFR< 60 mL/min/1.73m^2), hyperkalemia(> 5mMol/L) or congestive heart failure who are hypotensive (see 2 CONTRAINDICATIONS; and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS)).

pms-RAMIPRIL-HCTZ should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see 4 DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency (see 7 WARNINGS ANDPRECAUTIONS, Monitoring and Laboratory Tests, Renal Function Monitoring).

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at GFR values ≤30 mL/min per 1.73 m² body surface area (i.e., severe 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.

Respiratory

Acute Respiratory Distress
Severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms can include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, ALTACE HCT should be withdrawn and appropriate treatment should be given. ALTACE HCT must not be administered to patients who previously experienced ARDS following intake of hydrochlorothiazide or another thiazide diuretic.

Skin

Photosensitivity
Photosensitivity reactions have been reported with the use of thiazide diuretics. If the photosensitivity reactions occur during treatment with hydrochlorothiazide drugs, treatment should be stopped.

7.1 Special Populations

7.1.1 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, pms-RAMIPRIL-HCTZ should be discontinued as soon as possible, and, if appropriate, alternative therapy should be started. Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

The use of ACE inhibitors is contraindicated during pregnancy.

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

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.

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

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.

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

7.1.2 Breast-feeding

The presence of concentrations of ACE inhibitor and thiazides have been reported in human milk. The use of pms-RAMIPRIL-HCTZ is contraindicated during breastfeeding.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (>65 years of age): Because of decreased cardiovascular reserve, greater sensitivity in older patients (> 65 years) may be expected. Evaluation of renal function at beginning of treatment is recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3: Adverse Events occurring ≥ 1% in patients taking ramipril and hydrochlorothiazide (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

Adverse Events	Ramipril + HCT* n= 967 (%)	Ramipril n= 1058 (%)	HCT n= 515 (%)	Placebo n= 44 (%)
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 and hydrochlorothiazide tablets or ramipril + hydrochlorothiazide in combination.

8.3 Less Common Clinical Trial Adverse Reactions

Cardiac disorders: angina pectoris, palpitation, peripheral edema, tachycardia.

Ear and labyrinth disorders: hearing loss, tinnitus

Eye disorders: conjunctivitis, visual disturbances (including blurred vision).

Gastrointestinal disorders: abdominal pain (sometimes with enzyme changes suggesting pancreatitis), aphthous stomatitis, constipation, dry mouth, dyspepsia, dysphagia, gastroenteritis, gastritis, gastrointestinal pain, gingivitis, increased salivation, nausea, upper abdominal pain

General disorders and administration site conditions: chest pain, fever, shock

Hepatobiliary disorders: increased hepatic enzymes and/or conjugated bilirubin, cholestatic or cytolytic hepatitis. Calculous cholecystitis (due to hydrochlorothiazide)

Immune system disorders: allergic reactions

Metabolism and nutrition disorders: anorexia, decreased appetite, excessive thirst, gout, hyperglycemia, hyperuricemia, hypokalemia, weight gain (related to ramipril).

Musculoskeletal and connective tissue disorders: arthralgia, arthritis, myalgia.

Nervous system disorders: burning sensation (mainly to the skin of face or extremities), disorders of balance, neuropathy, paresthesia, polyneuritis, taste loss, tremor, vertigo.

Psychiatric disorders: anxiety, apathy, depression, insomnia, nervousness, sleep disorder, somnolence.

Renal and urinary disorders*:* abnormal kidney function, increase in urinary output (in connection with an improvement in cardiac performance), renal failure.

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: dyspnea, sinusitis.

Skin and subcutaneous tissue disorders: alopecia, angioedema, erythroderma, maculopapular rash, maculopapular exanthema, pruritus, psoriasis, purpura, rash, sweating.

Non-melanoma skin cancer
Some pharmacoepidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. Noting substantial uncertainty, a systematic review and meta-analysis undertaken by Health Canada suggested that the use of hydrochlorothiazide for several years (>3 years) could lead to:

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);
- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

Vascular disorders: hot flushes, hypotension, postural hypotension, syncope

8.4 Abnormal Hematologic and Clinical Chemistry Findings

Hematologic: decrease in red blood cell count, hemoglobin or hematocrit, leucocytosis.

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.

8.5 Post-Market Adverse Reactions

Blood and lymphatic system disorders: Agranulocytosis, bone marrow depression, eosinophilia, hemolytic anemia, reduction in the white blood cell or blood platelet count, neutropenia, pancytopenia. Hemoconcentration in the context of fluid depletion (see 7 WARNINGS AND PRECAUTIONS, Hematologic; and 9 DRUG INTERACTIONS).

Cardiac disorders: angina pectoris, cardiac arrhythmias, myocardial infarction, myocardial ischemia, palpitations, peripheral oedema, tachycardia.

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

Ear and labyrinth disorders: disturbed hearing, tinnitus.

Eye disorders: decreased lacrimation, visual disturbances, xanthopsia due to hydrochlorothiazide, choroidal effusion, acute myopia, acute angle-closure glaucoma (frequency not known).

Gastrointestinal disorders: abdominal discomfort, constipation, diarrhea, digestive disturbances, dryness of the mouth, gastric pain (including gastritic-like gastric pain), glossitis, inflammatory reactions of the oral cavity and gastrointestinal tract, diarrhea, increased levels of pancreatic enzymes, intestinal angioedema, nausea, pancreatitis (cases of fatal outcome have been very exceptionally reported), vomiting. Sialoadenitis due to hydrochlorothiazide.

General disorders and administration site conditions: asthenia, fatigue, fever, weakness.

Hepatobiliary disorders: cholestatic jaundice, hepatocellular damage, increases in serum levels of hepatic enzymes and/or bilirubin, liver damage (including acute liver failure).

Immune system disorders: anaphylactic or anaphylactoid reactions to ramipril or any of the other ingredients are rare (see 7 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. Increased antinuclear antibodies.

Metabolism and nutrition disorders: decline in serum sodium concentration; decrease in potassium concentration due to hydrochlorothiazide, dehydration, development or aggravation of a metabolic alkalosis, glycosuria (due to hydrochlorothiazide); hypochloremia, hypomagnesemia, hypercalcemia, increase in the concentration of serum potassium due to ramipril. General signs of disturbances in the electrolyte balance: confusion, drowsiness, headache, increased fluid excretion and muscle cramps.

Musculoskeletal and connective tissue disorders: arthralgia, muscle cramps, myalgia. Muscular weakness, musculoskeletal stiffness, tetany due to hydrochlorothiazide.

Nervous system disorders: cerebral ischemia (including ischaemic stroke and transient ischaemic attack), disorders of balance, dizziness, headache, impaired psychomotor skills (impaired reactions), light-headedness, paresthesia, smell, taste disturbances and tremor.

Psychiatric disorders: attention disturbances, confusion, depressed mood, feeling of anxiety, nervousness, restlessness, somnolence.

Renal and urinary disorders: 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).

Respiratory, thoracic and mediastinal disorders: bronchitis, bronchospasm (including aggravated asthma), dry (non-productive) tickling cough, dyspnea, nasal congestion, sinusitis.

Alveolitis allergic (pneumonitis), non-cardiogenic pulmonary oedema due to hydrochlorothiazide.

Acute respiratory distress syndrome (ARDS) due to hydrochlorothiazide.

Reproductive system and breast disorders: gynaecomastia, reduced libido, transient erectile impotence.

Skin and subcutaneous tissue disorders: alopecia, cutaneous or mucosal reactions such as rash, pruritus or urticaria, erythema multiforme, exacerbation of psoriasis, exfoliative dermatitis, maculopapular rash, pemphigoid or lichenoid exanthema or enanthema, pemphigus, photosensitivity, psoriasiform, Stevens-Johnson syndrome, sweating, systemic lupus erythematosus, toxic epidermal necrolysis.

Angioedema. Very exceptionally, the airway obstruction resulting from angioedema may have a fatal outcome.

System Organ Class: Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin and lip cancer (Basal cell carcinoma and Squamous cell carcinoma)

*Non-melanoma skin and lip cancer: Based on available data from two epidemiological studies based on Danish National cancer registries, cumulative dose-dependent association between HCTZ and non-melanoma skin and lip cancer (Basal cell carcinoma and Squamous cell carcinoma) has been observed (see 7 WARNINGS AND PRECAUTIONS, Non-melanoma skin cancer; and 10.2 Pharmacodynamics).

Vascular disorders: disturbed orthostatic regulation, exacerbation of perfusion disturbances due to vascular stenosis, hypotension, precipitation or intensification of Raynaud's phenomenon, syncope, thrombosis (in the context of severe fluid depletion), vascular stenosis, vasculitis.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

Consumption of alcohol while using pms-RAMIPRIL-HCTZ may potentiate the risk of orthostatic hypotension (see 9.4 Drug-Drug Interactions).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
ENTRESTO® (sacubitril/valsartan)	T	The concomitant use of an ACE inhibitor with ENTRESTO (sacubitril/ valsartan) is	Concomitant use with ENTRESTO® (sacubitril/valsartan) is contraindicated. Do not initiate pms-RAMIPRIL-HCTZ

Proper name	Ref	Effect	Clinical comment
		contraindicated, as the concomitant inhibition of neprilysin and ACE increases the risk of angioedema.	until 36 hours after the last dose of sacubitril/valsartan. In the case of a switch from pms-RAMIPRIL-HCTZ to sacubitril/valsartan, do not start sacubitril/valsartan until 36 hours after the last dose of pms-RAMIPRIL-HCTZ (see 2 CONTRAINDICATIONS; and 4 DOSAGE AND ADMINISTRATION).
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, thrombo test time and coagulation factors were not significantly changed.
Agents Causing Renin Release	T	Antihypertensive effect augmented.	The antihypertensive effect of ramipril is augmented by antihypertensive agents that cause renin release.
Agents Increasing Serum Potassium	CT	Since ramipril decreases aldosterone production, sometimes severe elevation of serum potassium may occur.	Potassium sparing diuretics such as spironolactone, triamterene or amiloride, potassium supplements, or other medicinal products that may increase kalemia should be given only for documented hypokalemia. Use with caution, including salt substitutes which contain potassium. Monitor serum potassium frequently.
Alcohol, barbiturates, or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates and narcotics especially with initiation of therapy.

Proper name	Ref	Effect	Clinical comment
Allopurinol, immuno-suppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood picture	T		Increased likelihood of hematological reactions.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Antacids	CT	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.	No effect
Antidiabetic agents (e.g., insulin and oral hypoglycemic)	CT	Hypoglycemic reactions with ACE inhibitors Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.	ACE inhibitors drugs may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycaemic reactions in patients concomitantly treated with antidiabetics. Therefore, monitor closely blood glucose particularly in the initial phase of co-administration. Monitor glycemic control, supplement potassium if necessary, to maintain Appropriate serum potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g., guanethidine, methyldopa, beta-	

Proper name	Ref	Effect	Clinical comment
		blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs, and direct renin inhibitors).	
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects. Increased hematological reactions may result from a combined effect of a cytotoxic agent and ACE inhibitor.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestrants, e.g., cholestyramine	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30- 35%.	Give thiazide 2-4 hours before or 6 hours after the bile sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and Increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Carbenoxolone, large amounts of liquorice, laxatives (in case of a prolonged use), and	T	Hypokalemia	Monitor potassium levels.

Proper name	Ref	Effect	Clinical comment
other kaliuretic agents			
Concomitant Diuretic Therapy	CT	Hypotensive effects	To minimize the possibility of hypotensive effects after the 1st dose of ramipril, discontinue the diuretic or increase the salt intake prior to initiation of treatment with ramipril. If it is not possible to discontinue the diuretic, the starting dose of ramipril should be reduced. The patient should be closely observed for several hours following the initial dose and until blood pressure has stabilized (see 7 WARNINGS AND PRECAUTIONS; and 4 DOSAGE AND ADMINISTRATION).
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur.	Monitor serum potassium levels and adjust medications, as required.
Desensitization therapy		The likelihood and severity of Anaphylactic and anaphylactoid reactions to insect venoma is increased under ACE inhibition.	It is assumed that this effect may also occur in connection with other allergens.
Digoxin	CT	In one open-label study in 12 subjects, administered multiple doses of both ramipril and digoxin, no changes were found in serum levels of ramipril, ramiprilat, and digoxin. Thiazide-induced electrolyte disturbances, i.e., hypokalemia, hypomagnesemia increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin closely. Supplement potassium or adjust doses of digoxin or thiazide, as required.
DDP-IV inhibitors (linagliptin, saxagliptin, sitagliptin		Patients taking concomitant DDP-IV inhibitor therapy may be	Caution should be used when initiating pms-RAMIPRIL-HCTZ in patients already taking a DPP- IV

Proper name	Ref	Effect	Clinical comment
		at increased risk for angioedema.	inhibitor or viceversa (see 7 WARNINGS AND PRECAUTIONS, Immune, Head and Neck Angioedema).
Drugs that alter GI motility, i.e., Anticholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretics may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Dual blockade of the Renin-Angiotensin-System (RAS)	CT, C	Dual Blockade of the Renin- Angiotensin System (RAS) with ACE inhibitors, including the ramipril component of pms-RAMIPRIL-HCTZ, ARBs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or moderate to severe renal impairment. The use of ACE inhibitors, including the ramipril lcomponent of pms-RAMIPRIL-HCTZ, in combination with an ARB is contraindicated inpatients with diabetic nephropathy. Further, co-administration of ACE inhibitors, including the ramipril component of pms-RAMIPRIL-HCTZ, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such	See 2 CONTRAINDICATIONS; and 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).

Proper name	Ref	Effect	Clinical comment
		treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	
Gold	CS	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and symptomatic hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ramipril.	
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RCS	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The coadministration hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dose adjustment of gout medications may be required.
Heparin	T	Rise in serum potassium concentration possible.	
Lithium	CT	Thiazide diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity. Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium.	Concomitant use of thiazide diuretics with lithium is generally not recommended. If These drugs must be used together, decrease lithium dose by 50% with close monitoring of lithium concentration, serum electrolytes and fluid intake. If a diuretic is also used, the risk of lithium toxicity maybe further increased.
Methyldopa	T	Hemolysis possible	
Neprilysin (NEP)	T	ACE inhibitors are known	Caution should be used when

Proper name	Ref	Effect	Clinical comment
inhibitors		to cause angioedema. This risk may be elevated when used concomitantly with a neutral endopeptidase inhibitor	initiating pms-RAMIPRIL-HCTZ in patients already taking a neutral endopeptidase inhibitor or vice versa (see 7 WARNINGS AND PRECAUTIONS, Immune, Head and Neck Angioedema).
Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid	CT	The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs (e.g., indomethacin). Concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening renal function and an increase in serum potassium. NSAID-related retention of sodium and water antagonizes the diuretic and antihypertensive effects of thiazides. NSAID-induced inhibition of renal prostaglandins leading to decreases of renal blood flow, along with thiazide-induced decreases in glomerular filtration rate (GFR) may lead to acute renal failure. Patients with heart failure may be at particular risk.	Avoid if possible. If not possible, close monitoring of serum creatinine, potassium and patient's weight is recommended. Observe the patient to ensure diuretic effects are obtained. Monitor blood pressure and renal function. Increase dose if necessary or discontinue NSAID.
Other substances with antihypertensive potential (e.g., nitrates)	T	Potentiation of the antihypertensive effect is to be anticipated.	
Salt	T	Possible attenuation of the antihypertensive effect by increased dietary salt intake.	

Proper name	Ref	Effect	Clinical comment
Selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, e.g., tubocurare	C	Thiazide drugs may increase the responsiveness of skeletal muscle relaxants, such as curare derivatives. 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.
Sympathomimetics	T	Reduce the 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. Particularly close blood pressure monitoring is recommended.
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate supplements or adjust topiramate dose as necessary.
mTOR inhibitors (e.g., sirolimus, everolimus, temsirolimus):	C	An increased incidence of angioedema was observed in patients taking ACE inhibitors and mTOR	Caution should be used when initiating pms-RAMIPRIL-HCTZ in patients already taking mTOR inhibitors or vice versa (see 7

Proper name	Ref	Effect	Clinical comment
		inhibitors (mammalian target of rapamycin inhibitors).	WARNINGS AND PRECAUTIONS, Head and Neck Angioedema).
Warfarin		No alteration of the anticoagulant effects with ramipril.	

Legend: C=Case Study; RCS=Retrospective Cohort Study; CT= Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ramipril and hydrochlorothiazide tablets have 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 7 WARNINGS AND PRECAUTIONS, Metabolism).

10.2 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 (BP) without a compensatory rise in heart rate.

In most patients, the onset of the antihypertensive effect of a single dose becomes apparent 1- 2 hours after oral administration. The peak effect of a single dose is usually reached 3- 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 BP.

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

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

10.3 Pharmacokinetics

Table 5: Summary of pharmacokinetic parameters after single doses of 5/25 mg ramipril and hydrochlorothiazide tablets, 5 mg ramipril, 25 mg hydrochlorothiazide (HCT) or 5 mg ramipril + 25 mg HCT from study HOE9829/1502

Arithmetic Mean (CV%) (Geometric LS Mean)				
Substrate	**Cmax [ng/mL]**	**Tmax [h]**	**AUCT [ng*h/mL]**	**AUC (0-72) [ng*h/mL]**
Ramipril/ hydrochlorothiazide 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)
hydrochlorothiazide 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 hydrochlorothiazide 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 ≥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- 4 hours after oral administration of ramipril.

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

Metabolism
The prodrug ramipril undergoes an extensive hepatic first pass metabolism (hydrolysis), which is essential for the formation of the sole active metabolite ramiprilat. 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- 90% of the metabolites in urine and bile have been identified as ramiprilat or ramiprilat metabolites. Ramipril glucuronide and ramipril diketopiperazine represented approximately 10- 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- 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- 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 7 WARNINGS AND PRECAUTIONS, Renal).

Hydrochlorothiazide

Absorption
The bioavailability of hydrochlorothiazide after oral administration is approximately 70%.

Distribution
Approximately 40% of hydrochlorothiazide is bound to plasma proteins.

Metabolism
Hydrochlorothiazide undergoes negligible hepatic metabolism and has not been shown to induce or inhibit any CYP450 isoenzymes.

Excretion
Hydrochlorothiazide is excreted almost entirely (>95%) by renal route in unchanged form. After oral administration of a single dose, 50-70% is excreted within 24 hours.

The elimination half-life is 5- 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

Geriatrics (> 65 years of age)
In healthy subjects aged 65- 76 years, ramipril and ramiprilat kinetics are similar to those in healthy young subjects.

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.

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.

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 7 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 < 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 4 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 <30- 50 mL/min.

11 STORAGE, STABILITY AND DISPOSAL

Store pms-RAMIPRIL-HCTZ (ramipril/hydrochlorothiazide) between 15℃ - 30℃. Protect from heat and humidity.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for pms-RAMIPRIL-HCTZ.

PART II : SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

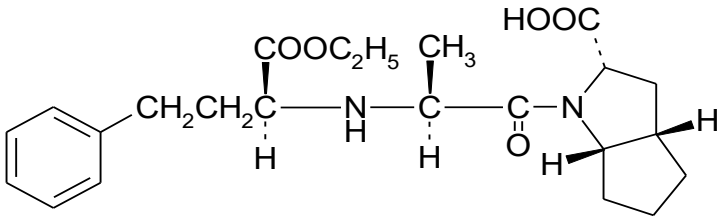
Proper name: Ramipril

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

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

Molecular formula and molecular mass: $C_{23}H_{32}N_2O_5$ 416.52 g/mol

Structural formula:



Physicochemical properties:

Description: A white to off-white crystalline powder

Melting point: 105℃ to 112℃

Solubility: Slightly soluble in water, and freely soluble in ethanol and methanol.

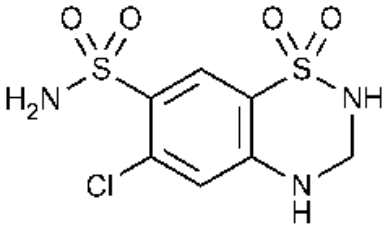
Drug Substance

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: $C_7H_8ClN_3O_4S_2$ 297.72 g/mol

Structural formula:



Physicochemical properties:

Description: A white or almost white, crystalline powder

Solubility: Very slightly soluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The Treatment of Essential Hypertension in Patients for Whom this Combination Therapy is Appropriate

Table 6: Summary of patient demographics for clinical trials in specific indication

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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 /201/ 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	R: 93/75 non-responders: 35 H: 99/78 non-responders: 49	56 (29-80)	99/93

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
		16 weeks			
HOE498/8/ USA/351/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: 5/25mg/ od Oral 12 weeks	R: 120/111 H: 120/114 R+H: 120/113	(27-80)	238/122
HOE498/2/ MN/309/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/MN /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/310/HT (Study 4)	Open-label, uncontrolled, multicentre, one-year extension of HOE498/2/MN /309/HT (Study 3)	Responders: R: 5 mg/od Non-responders: 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, which 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- 4.

Table 7: 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 H: 12.5 mg R+H: 2.5/12.5 mg	218/185 220/183 222/167	166.7/102.2 167.9/102.9 167.5/102.1		149.3/89.1 149.3/90.4 147.4/87.8			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.
HOE498 – 201HT (Study 1)	R: 2.5 mg R: 5 mg R: 10 mg H: 12.5 mg H: 25 mg R+H: 2.5/12.5 mg R+H: 2.5/25 mg R+H: 5/12.5 mg R+H: 5/25 mg R+H: 10/12.5 mg R+H: 10/ 25 mg	44/44 48/47 44/43 46/45 42/40 45/42 43/42 44/44 47/44 43/43 44/42	162.5/106.4 161.0/106.0 157.4/107.1 161.3/107.2 161.0/106.6 160.1/106.1 163.0/105.9 161.8/106.8 163.8/108.1 158.7/106.6 163.9/106.4	153.3/99.7 149.1/100.0 146.2/98.6 152.6/100.7 149.1/98.2 145.0/97.2 147.1/97.2 144.0/95.9 143.4/94.7 141.1/93.6 142.9/95.1				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.
HOE498 – 302HT (Study 5)	Responders: R: 10 mg H: 50 mg	30 45	Phase 1: 166.4/102.8	148.7/84.7 143.5/84.8			148.8/84.5 139.4/83.2	Change in	The results are for the second phase(weeks 11 – 16), except for the

Table 7: 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.**		
	Non-responders: R+H: 10/ 50 mg	84	167.6/101.9 (N=129)	160.4/99.1			149.5/90.85	Systolic and diastolic Supine and standing blood pressure.	baseline blood pressure values. In the second phase, responders continued with monotherapy and non-responders were placed on combination therapy.
HOE498 – 351HT (Study 2)	R: 5 mg H: 25 mg R+H: 5/ 25 mg	120/111 120/114 120/113	157.3/104.4 159.7/104.2 158.1/104.4	152.2/98.1 145.4/93.9 141.8/91.9				Change in Systolic and diastolic Supine and standing blood pressure.	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.
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 R: 10 mg R+H: 5/ 25 mg	54/53 53/50 58/57	171.5/103.2 174.2/102.7 176.0/102.5			152.8/90.6 152.1/89.6 149.0/87.0			
HOE9829 – 201HT (Study 6)	R+H: 5/25 mg R+H: 10/ 50 mg	73/73 3/3 9/9	Not available, since this is a					Change in Systolic and diastolic Supine and	There was no evidence of an increase in mean

Table 7: 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.**		
	SWITCH (R+H): 5/25 or 10/50 mg		one-year extension.					standing blood pressure	blood pressure or of an increase in the number of non-responders during long-term treatment.
HOE498 – 310HT (Study 4)	R: 5 mg R+H: 5/25 mg SWITCH (R or R+H): 5 mg or 5/ 25 mg	38/31 83/81 38/32						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= Ramipril

H= Hydrochlorothiazide (HCT)

14.3 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 Pharmascience Inc. pms-RAMIPRIL-HCTZ 10 mg/25 mg tablets versus the reference product, ALTACE HCT® 10 mg/25 mg Tablets, by Sanofi Aventis Canada Inc. The pharmacokinetic data calculated for the pms-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 10 mg/25 mg 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)		

*pms-RAMIPRIL-HCTZ, Pharmascience Inc., Montréal, Canada
†ALTACE HCT®, Sanofi Aventis Canada Inc., 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 10 mg/25 mg 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)	1,034.01 1,061.91 (19.9)	1,057.46 1,092.35 (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)		

*pms-RAMIPRIL-HCTZ, Pharmascience Inc., Montréal, Canada
†ALTACE HCT®, Sanofi Aventis Canada Inc., Laval, Québec, Canada
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV %)

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute toxicity

Ramipril
As it has an LD_{50} >10,000 mg/kg body weight in mice and rats and >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 >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 on 40 mg/kg body weight lead to shifts in plasma electrolytes and to anaemia. At daily doses of ≥3.2 mg/kg body weight, 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. 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.

Ramipril + Hydrochlorothiazide

Rats
In studies on embryotoxicity, the combination was administered to rats in daily doses of 1- 2400 mg/kg body weight during the sensitive phase of organogenesis. Hydrochlorothiazide has been studied in a similar way alone at daily doses of 125-2000 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 ≤10 mg/kg body weight without complications. Doses of ≥150 mg/kg body weight 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, 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.

A dose of 1 mg/kg body weight does not impair the development of the embryo. Doses of ≥10 mg/kg body weight 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, 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, at levels of ≥600 mg/kg body weight, 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 2 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 –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 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.

Hydrochlorothiazide
According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the highest dose and adrenal pheocytochroma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

The mutagenic potential was assessed in a series of *in vitro* and *in vivo* test systems. While some positive results were obtained *in vitro*, all *in vivo* studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers in vitro and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential *in vivo*, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

17 SUPPORTING PRODUCT MONOGRAPHS

[Pr]ALTACE HCT® (Ramipril and Hydrochlorothiazide Tablets, 2.5/12.5 mg, 5/12.5 mg, 10/12.5 mg, 5/25 mg, 10/25 mg), submission Control No.: 265837, Product Monograph, Bausch Health, Canada Inc., January 6, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-RAMIPRIL-HCTZ
Ramipril and Hydrochlorothiazide Tablets

Read this carefully before you start taking **pms-RAMIPRIL-HCTZ** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-RAMIPRIL-HCTZ**.

Serious Warnings and Precautions

Pregnancy: Angiotensin converting enzyme (ACE) inhibitors, such as pms-RAMIPRIL-HCTZ, can cause harm or even death to your unborn baby. Therefore, pms-RAMIPRIL-HCTZ should not be taken during pregnancy. If you become pregnant or think you are pregnant, stop taking pms-RAMIPRIL-HCTZ right away and tell your healthcare professional.

What is pms-RAMIPRIL-HCTZ used for?
pms-RAMIPRIL-HCTZ is used in adults to treat essential hypertension (high blood pressure).

How does pms-RAMIPRIL-HCTZ work?
pms-RAMIPRIL-HCTZ is a combination tablet of two medical ingredients, ramipril and hydrochlorothiazide. Ramipril is an angiotensin converting enzyme (ACE) inhibitor that widens blood vessels. While, hydrochlorothiazide is a diuretic or “water pill” that increases the amount of urine output. These work together to lower high blood pressure.

What are the ingredients in pms-RAMIPRIL-HCTZ?
Medicinal ingredients: Ramipril and hydrochlorothiazide.

Non-medicinal ingredients:
- **10 mg/12.5 mg tablets:** Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Lactose Monohydrate, Microcrystalline Cellulose, Red Iron Oxide, Sodium, Stearyl Fumarate, and Yellow Iron Oxide.
- **10 mg/25 mg tablets:** Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Lactose Monohydrate, Microcrystalline Cellulose, Red Iron Oxide Sodium, Stearyl Fumarate,.

pms-RAMIPRIL-HCTZ comes in the following dosage forms:
Tablets:
- 10 mg ramipril/12.5 mg hydrochlorothiazide
- 10 mg ramipril/25 mg hydrochlorothiazide

Do not use pms-RAMIPRIL-HCTZ if:

- you are allergic to ramipril, hydrochlorothiazide, or any of the other ingredients in pms-RAMIPRIL-HCTZ.
- you are allergic to any other ACE inhibitors, other thiazide diuretics, or sulfonamides.
- you have a personal or family history of angioedema (swelling of tissue under the skin).
- you are pregnant or planning to become pregnant.
- you are breastfeeding or planning to breastfeed.
- you have renal artery stenosis (narrowing of the arteries to one or both kidneys).
- you have hypotension (low blood pressure).
- you have taken ENTRESTO® (sacubitril and valsartan) within the last 36 hours, or are currently taking ENTRESTO®.
- you have anuria (difficulty urinating or producing no urine).
- you have severe kidney problems.
- you are receiving hemodialysis or hemofiltration with high-flux membranes (e.g., polyacrylonitrile) treatment. These treatments are used to remove certain molecules from the blood.
- you are on low-density lipoprotein (LDL) apheresis with dextran sulfate (a treatment used to remove LDL cholesterol from the blood).
- you have severe liver problems.
- you have electrolyte disturbances such as:
  - hypokalemia(low potassium in the blood),
  - hyponatremia(low sodium in the blood), or
  - hyperkalemia(high potassium in the blood).
- you are taking medicines that contain aliskiren (such as RASILEZ®) that are used to lower blood pressure or angiotensin II receptor antagonists (ARBs) that are used to treat high blood pressure and have one of the following conditions:
  - diabetes with end organ damage
  - kidney disease
  - high potassium levels
  - heart failure combined with low blood

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-RAMIPRIL-HCTZ. Talk about any health conditions or problems you may have, including if you:

- have heart problems.
- have diabetes.
- have liver problems.
- have kidney problems.
- have a kidney transplant.
- are allergic to penicillin.
- have recently received or are planning to get allergy shots for bee or wasp stings.
- have a personal or family history of cancer.

- are at a higher risk of developing skin cancer. You may be at a higher risk if you have light skin colour, have a personal or family history of skin cancer, or if you are taking medicines that suppress your immune system.
- are planning to have surgery or anesthesia.
- have a history of bronchial asthma.
- have lupus erythematosus (an autoimmune disease) or gout (a type of arthritis that causes joint pain).
- have Raynaud's phenomenon (a condition resulting from poor circulation in the extremities, such as fingers and toes). It may begin or worsen.
- have scleroderma (a disease that can cause thickening, hardening, or tightening of the skin, blood vessels and internal organs).
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are on a low-salt diet.
- have had breathing or lung problems (including inflammation or fluid in the lungs) in the past following the use of medication containing hydrochlorothiazide or certain diuretics (i.e., "water pills"). If you experience any severe shortness of breath or difficulty breathing after taking ALTACE HCT, stop the medication and seek medical attention immediately.

Other warnings you should know about:

pms-RAMIPRIL-HCTZ can cause the following:

- **Skin cancer:** Hydrochlorothiazide in pms-RAMIPRIL-HCTZ may increase the risk of developing skin cancer such as non-melanoma skin cancer (NMSC), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC). The risk is higher if you have been taking pms-RAMIPRIL-HCTZ for many years (more than 3) or at a high dose. While taking pms-RAMIPRIL-HCTZ:
  - you should regularly check your skin for new lesions (e.g., a lump, bump, sore, or patch). These are more likely to occur in areas that are more exposed to the sun (e.g., face, ears, hands, shoulders, upper chest, and back).
  - you should limit your exposure to the sun, avoid indoor tanning, and use sun protection when going outside. This includes using sunscreen (SPF 30 or higher), wearing protective clothing, and wearing a hat.
  - tell your doctor right away if you get more sensitive to the sun or UV light, or if you develop an unexpected lesion.

- **Hypotension (low blood pressure):** Treatment with pms-RAMIPRIL-HCTZ can cause hypotension. Your healthcare professional may monitor your health and adjust your dose as needed. Tell your healthcare professional, if you notice an increase in sweating, feel dehydration, are vomiting, or have diarrhea.

- **Blood problems:** Treatment with ACE inhibitors, such as pms-RAMIPRIL-HCTZ, can cause:
  - agranulocytosis (decrease in white bloods cells),
  - neutropenia (decreased white blood cells), or
  - leukopenia (decreased white blood cells).

If you notice any signs of these blood problems including infections, tell your healthcare professional right away.

- **Liver problems:** Treatment with ACE inhibitors, such as pms-RAMIPRIL-HCTZ, can cause liver problems such as:
  - hepatitis (inflammation of the liver),
  - jaundice (yellowing of the skin or whites of eyes), and
  - liver failure.

  If you notice any symptoms of liver problems, especially within the first weeks or months of treatment, tell your healthcare professional. You may also be tested to assess your liver function before, during, and after your treatment with pms-RAMIPRIL-HCTZ. This will help them decide if you should reduce or stop your dose.

- **Kidney problems:** Treatment pms-RAMIPRIL-HCTZ can cause kidney problems resulting in decreased urine, progressive azotemia (high levels of nitrogen in the blood), kidney failure or even death. Your healthcare professional will closely monitor your kidneys before and during your treatment. They may decide to reduce or stop your treatment.

- **Angioedema (swelling of tissue under the skin)**: Treatment with ACE inhibitors, such as pms-RAMIPRIL-HCTZ, can cause angioedema that can be life-threatening. Your healthcare professional will monitor your health for signs of angioedema. If you notice swelling on your body or have difficulty swallowing or breathing, stop taking pms-RAMIPRIL-HCTZ and tell your healthcare professional right away.

- **Fluid or electrolyte imbalance**: Hydrochlorothiazide in pms-RAMIPRIL-HCTZ can cause fluid or electrolyte imbalances such as:
  - hypokalemia(low potassium in the blood),
  - hyponatremia(low sodium in the blood),
  - hypochloremic alkalosis (low chloride in the blood),
  - hyperuricemia (high uric acid in the blood), and
  - acute gout (a type of arthritis that causes joint pain).

  Tell your healthcare professional if you notice any signs or symptoms related to fluid or electrolyte imbalances.

- **Photosensitivity:** You may become sensitive to the sun while taking pms-RAMIPRIL-HCTZ. Exposure to sunlight should be reduced until you know how you respond. Tell your healthcare professional if you notice any photosensitivity. They may decide to stop your treatment with pms-RAMIPRIL-HCTZ.

- **Eye problems:** Hydrochlorothiazide in pms-RAMIPRIL-HCTZ can cause sudden eye disorders:
  - **Choroidal effusion** (an abnormal build-up of liquid in your eye that may result in vision changes),
  - **Myopia:** (sudden nearsightedness or blurred vision), and

- **Glaucoma** (an increased pressure in your eye, eye pain. Untreated, it may lead to permanent vision loss).

If your vision changes, stop taking pms-RAMIPRIL-HCTZ and seek immediate medical help. These eye disorders are related and can develop within hours to weeks of starting pms-RAMIPRIL-HCTZ.

See the **Serious side effects and what to do about them table**, below, for more information on these and other serious side effects.

Driving and using machines: pms-RAMIPRIL-HCTZ can decrease your blood pressure causing light-headedness, dizziness, and fainting. These can occur more often after your first dose, and when your dose is increased. Before you drive or do tasks that require special attention, wait until you know how you respond to pms-RAMIPRIL-HCTZ.

Check-ups and testing:
- You may have regular visits with your healthcare professional, before, during and after your treatment. These tests may be used to monitor your health such as your kidney function, liver function, and the profile of your blood.
- pms-RAMIPRIL-HCTZ can affect the level of calcium within your blood. Your healthcare professional may stop your treatment with pms-RAMIPRIL-HCTZ before performing tests that assess the function of your parathyroid glands.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with pms-RAMIPRIL-HCTZ:
- other medicines used to lower high blood pressure such as methyldopa.
- medicines known as diuretics ("water pill") such as potassium-sparing diuretic and potassium-retaining diuretics (e.g., spironolactone, triamterene, or amiloride).
- medicines that increase the potassium in the blood such as a salt substitute that contains potassium, potassium supplements, and a potassium-sparing diuretic (a type of "water pill").
- medicines that may change the profile of your blood such as immunosuppressants (used to lower the body's ability to reject a transplanted organ), procainamide (used to treat irregular heartbeats), and cytostatic medicines (used to treat certain types of cancer).
- medicines used to treat fungal infections such as Amphotericin B.
- medicines used to treat cancer such as cyclophosphamide and methotrexate.
- medicines used to lower cholesterol such as bile acid resins.
- medicines used to treat epilepsy such as carbamazepine and topiramate.
- medicines used to treat acid peptic disease such as carbenoxolone.
- medicines known as laxatives that are used to loosen stool or help a bowel movement.
- medicines used to help with sleep such as barbiturates.
- medicines used to help reduce intense pain such as narcotics.
- vitamins and mineral supplements such as calcium or vitamin D.

- medicines known as corticosteroids that are used to treat joint pain, swelling, and other conditions.
- medicines used to treat West Syndrome such as adrenocorticotropic hormone (ACTH).
- medicines used to decrease the effects from allergens (allergy shots).
- medicines used to treat heart conditions such as digoxin.
- medicines used to treat diabetes (antidiabetic) such as insulin, gliptins (e.g., sitaglitin, linagliptin, saxagliptin), and oral hypoglycemic agents (used to lower glucose levels in the blood).
- medicines that change the speed of bowel movements such as atropine, metoclopramide, and domperidone.
- gold used to treat arthritis (swelling and tenderness of joints).
- medicines used to treat gout (a type of arthritis that causes joint pain) such as allopurinol, probenecid, uricosurics, and xanthine oxidase inhibitors.
- medicines used to treat and prevent blood clots such as heparin.
- medicines used to treat bipolar disease such as lithium.
- medicines known as neutral endopeptidase (NEP) inhibitors. If you are unsure ask your healthcare professional.
- nonsteroidal anti-inflammatory drugs (NSAIDs) that are used to reduce pain and swelling such as ibuprofen, naproxen, celecoxib, indomethacin, and acetylsalicylic acid (aspirin).
- medicines that have the potential to lower blood pressure such as nitrates.
- medicines used to treat depression (antidepressants) such as selective serotonin re - uptake inhibitors (e.g., citalopram, escitalopram, and sertraline).
- medicines used to relieve muscle spasms such as tubocurare.
- medicines known as sympathomimetic agents that reduce nasal congestion such as cough and cold medicines.
- medicines known as mammalian target of rapamycin (mTOR) inhibitors such as sirolimus, temsirolimus, and everolimus. These are used to lower the body's ability to reject a transplanted organ or to treat certain types of cancer.
- alcohol.
- large amounts of liquorice.

How to take pms-RAMIPRIL-HCTZ:

- pms-RAMIPRIL-HCTZ is not for initial therapy.
- You must be stabilized on ramipril and hydrochlorothiazide before taking pms-RAMIPRIL-HCTZ. If your dosage matches the dosages in pms-RAMIPRIL-HCTZ, your healthcare professional may prescribe pms-RAMIPRIL-HCTZ (instead of each medicinal ingredient as a separate pill).
- Your healthcare professional will decide the dose and length of pms-RAMIPRIL-HCTZ for you. They may start with a low dose and slowly adjust the dose as needed. Take pms-RAMIPRIL-HCTZ exactly as prescribed by your healthcare professional.
- pms-RAMIPRIL-HCTZ can be taken with or without food. The tablet(s) should be swallowed whole with liquid (approximately half a glass). Do NOT chew or crush the tablets. If pms-RAMIPRIL-HCTZ causes upset stomach, take it with food or milk.

- It is recommended that your daily dose is taken about the same time every day in the morning.
- Your healthcare professional will monitor your health throughout your treatment and may interrupt, reduce or stop your dose.

Usual dose:
The usual daily dose is 2.5 mg/12.5 mg of ramipril and hydrochlorothiazide. The maximum daily dose is 10 mg/50 mg of ramipril and hydrochlorothiazide.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-RAMIPRIL-HCTZ, contact a healthcare professional, hospital emergency department, or regional Poison control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take it as soon as you remember. However, if it is almost time for your next dose, do not take the missed dose. Instead, take your next scheduled regular dose. Do not double your dose at any time.

What are possible side effects from using pms-RAMIPRIL-HCTZ?
These are not all the possible side effects you may have when taking pms-RAMIPRIL-HCTZ. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- difficulty in maintaining your balance while standing
- cough
- upset stomach
- constipation
- flushing of the skin
- runny or stuffy nose
- bronchitis (inflammation of the lining of your lungs)
- swollen lymph nodes
- mouth ulcer
- tongue pain
- attention disturbances
- problems with sleeping
- sexual difficulties
- impotence
- reduced libido
- breast enlargement in men
- hearing, taste or smell changes
- loss of hair
- back pain

- eye modification (pink eye, less tearing, yellow vision)
- inflammation or enlargement of salivary glands
- Raynaud's phenomenon (episodes of reduced blood flow)

Tell your healthcare professional if any of these affects you severely.

Serious side effects and what to do about them			
Symptom/ Effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Hypotension (low blood pressure)**:** dizziness, fainting, light-headedness (may occur when you go from lying or sitting to standing up), blurred vision, nausea, vomiting, or fatigue	✓		
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness, generally feeling unwell, muscle spasms, cramping, constipation, feeling of skipped heart beats or palpitations, fatigue, tingling, or numbness		✓	
Non-melanoma skin cancer: lump or discoloured patch on the skin that stays after a few weeks and slowly changes; lumps can be red/pink, firm and sometimes turn into ulcers; and cancerous patches are usually flat and scaly		✓	
Neuralgia (pain that follows the path of the nerve): sudden attacks of severe sharp shooting pain		✓	
UNCOMMON			
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, effect on the eyes, itching, fever, wheezing, drop in blood pressure, or feeling sick to your stomach and throwing up			✓
Tachycardia (abnormally fast heartbeat)			✓
Myocardial infarction (heart attack)**:** pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light- headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, palpitations, or possible irregular heartbeat			
Stroke (bleeding or blood clot in the brain)**:** sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden			✓

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
headache, blurry vision, difficulty swallowing or speaking, lethargy, dizziness, fainting, vomiting, trouble understanding, or trouble with walking and loss of balance			
Angioedema (swelling of tissue under the skin)**:** abdominal pain (with or without nausea or vomiting), difficulty breathing, swollen face, hands and feet, genitals tongue, throat, swelling of the digestive tract causing diarrhea, nausea, or vomiting			✓
Behavior and mood changes: depression (sad mood that won't go away), nervousness, difficultly sleeping or sleeping too much, or confusion			
Bronchospasm (when there is a sudden narrowing of the airway): difficulty breathing with wheezing, or coughing			✓
Kidney problems: increased or decreased urination, nausea, vomiting, swelling of extremities, fatigue, fever, thirst, dry skin, irritability, dark urine, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, or mental status changes (drowsiness, confusion, coma)		✓	
Liver problems: yellowing of the skin or eyes (jaundice), dark urine, abdominal pain or swelling, nausea, vomiting, loss of appetite, or unusual tiredness		✓	
Hyperglycemia (high blood sugar)**:** frequent urination, thirst, and hunger, dry skin, headache, blurred vision, or fatigue	✓		
Electrolyte imbalance: weakness, drowsiness, muscle pain or cramps, or irregular heartbeat		✓	
RARE			
Decreased platelets: bruising, bleeding, fatigue, or weakness		✓	
Decreased white blood cells: infections, fatigue, fever, aches, pains, or flu-like symptoms		✓	
VERY RARE			
Toxic Epidermal Necrolysis (TEN) (severe skin reaction)**:** redness, blistering and/or peeling of large areas of the skin			✓

Serious side effects and what to do about them			
Symptom/ Effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Acute respiratory distress (inflammation of lung tissue or excess fluid in the lungs): severe shortness of breath or difficulty breathing, fever, weakness, and confusion			✓
UNKNOWN FREQUENCY			
Eye disorders: **Myopia:** sudden near sightedness or blurred vision **Glaucoma:** increased pressure in your eyes, or eye pain **Choroidal effusion** (build-up of liquid in your eye): blind spots, eye pain, or blurred vision			✓
Anemia (decreased number of red blood cells)**:** fatigue, loss of energy, weakness, shortness of breath, irregular heartbeats, or pale complexion		✓	
Pancreatitis (inflammation of the pancreas): upper abdominal pain that lasts and gets worse when you lie down, nausea, vomiting, fever, rapid heartbeat, or tenderness when touching the abdomen		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15°C and 25°C. Protect from heat and humidity.

Keep out of the reach and sight of children.

If you want more information about pms-RAMIPRIL-HCTZ:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by calling the manufacturer Pharmascience Inc., at 1-866-550-6060.

This leaflet was prepared by:

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