PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**ACCURETIC®**

Quinapril (as hydrochloride) and Hydrochlorothiazide

10/12.5 mg, 20/12.5 mg and 20/25 mg tablets

Angiotensin Converting Enzyme Inhibitor/Diuretic

®Parke, Davis & Company LLC

Pfizer Canada ULC, Licensee
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Kirkland, Quebec H9J 2M5

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACCURETIC (quinapril hydrochloride and hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate.

ACCURETIC is not indicated for initial therapy. Patients in whom quinapril and hydrochlorothiazide are initiated simultaneously can develop symptomatic hypotension (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, - Hypotension and 9 DRUG INTERACTIONS).

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

1.1 Pediatrics (<18 years of age)

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (> 65 years of age)

Therapeutic effects appear to be the same for elderly (>65 years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

2 CONTRAINDICATIONS

ACCURETIC is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme (ACE) inhibitor (see 7 WARNINGS AND PRECAUTIONS, General, Angioedema).
- Combination with sacubitril/valsartan due to increased risk of angioedema. ACCURETIC must not be initiated until at least 36 hours have elapsed following discontinuation of sacubitril/valsartan therapy. If treatment with ACCURETIC is stopped, sacubitril/valsartan therapy must not be initiated until 36 hours after the last dose of ACCURETIC.
- Patients hypersensitive to other sulfonamide-derived drugs because of the hydrochlorothiazide component.
- Patients with anuria.
- Women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women and 8 ADVERSE REACTIONS).

- Nursing women (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.2 Breast-feeding).
- Combination with aliskiren-containing medicines in patients with:
    - diabetes mellitus (type 1 or type 2),
    - moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2),
    - hyperkalemia (> 5 mMol/L) or
    - congestive heart failure who are hypotensive (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual blockade of the Renin-Angiotensin System (RAS) and Renal, Renal Impairment, and 9 DRUG INTERACTIONS, Aliskiren-containing medicines and Angiotensin receptor blockers (ARBs)).
- Combination with angiotensin receptor blockers (ARBs) in patients with:
    - diabetes mellitus (type 1 or type 2) with end organ damage,
    - moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73m^2),
    - hyperkalemia (> 5mMol/L)
    - congestive heart failure who are hypotensive (see 9 DRUG INTERACTIONS, Angiotensin receptor blockers (ARBs)).
- Patients with the rare hereditary condition of galactose intolerance, glucose-galactose malabsorption or Lapp lactase deficiency as ACCURETIC contains lactose (see 7 WARNINGS AND PRECAUTIONS, Sensitivity/Resistance).

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. When pregnancy is detected, ACCURETIC should be discontinued as soon as possible.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Dosage of ACCURETIC must be individualized. The fixed combination is not for initial therapy. The dose of ACCURETIC (quinapril hydrochloride and hydrochlorothiazide) should be determined by titration of the individual components.

Once the patient has been successfully titrated with the individual components as described below, ACCURETIC may be substituted if the titrated doses and dosing schedule can be achieved by the fixed combination (see 1 INDICATIONS and 7 WARNINGS AND PRECAUTIONS). In some patients, a twice daily administration may be required.

Patients do not generally require hydrochlorothiazide (HCTZ) in excess of 50 mg daily,

particularly when combined with other antihypertensive agents.

4.2 Recommended Dose and Dosage Adjustment

Quinapril Monotherapy: The recommended initial dose of quinapril in patients not on diuretics is 10 mg once daily. An initial dose of 20 mg once daily can be considered for patients without advanced age, renal impairment, or concomitant heart failure and who are not volume depleted (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension). Dosage should be adjusted according to blood pressure (BP) response, generally at intervals of 2-4 weeks. A dose of 40 mg daily should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring BP just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either 2x daily administration with the same total daily dose, or an increase in dose should be considered. If BP is not controlled with quinapril alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of quinapril.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of quinapril and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for 2-3 days before beginning therapy with quinapril to reduce the likelihood of hypotension (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension). If the diuretic cannot be discontinued, an initial dose of 5 mg of quinapril should be used with careful medical supervision for several hours and until BP has stabilized. The dosage of quinapril should subsequently be titrated (as described above) to the optimal response.

If a diagnosis of acute respiratory distress syndrome (ARDS) is suspected, ACCURETIC should be withdrawn and appropriate treatment given.

Dosage Adjustment in Renal Impairment: For use in hemodialysis patients, see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS, Anaphylactoid Reactions during Membrane Exposure. Quinapril should be administered on days when dialysis is not performed.

Starting doses should be reduced according to the following guidelines:

Table 1 – Guidelines for starting doses

Creatinine Clearance (mL/min)	Maximum Recommended Initial Dose (mg)
>60	10
30-60	5
10-30	2.5
<10	Insufficient data for dosage recommendation

Patients should subsequently have dosage titrated (as described above) to the optimal

response as described under Monotherapy.

When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic rather than a thiazide is preferred for use with quinapril. Therefore, for patients with severe renal dysfunction, ACCURETIC is not recommended.

Dosage in the Elderly: The recommended initial dosage of quinapril is 10 mg once daily (depending on renal function), followed by titration to the optimal response as described above under Monotherapy.

4.3 Administration

See 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment

4.4 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, the missed dose should be skipped. The patient should be cautioned against taking two doses concomitantly to "make up" for the missed dose.

5 OVERDOSAGE

No data are available regarding overdosage with ACCURETIC or quinapril. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should be normally treated by intravenous volume expansion with 0.9% sodium chloride. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

The most common signs and symptoms observed for HCTZ monotherapy overdosage are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet: 10/12.5, 20/12.5 and 20/25 mg	Candelilla wax, crospovidone, lactose, magnesium carbonate, magnesium stearate, povidone, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

ACCURETIC (quinapril hydrochloride and hydrochlorothiazide) is available as fixed combination tablets in 3 strengths of quinapril hydrochloride with hydrochlorothiazide:

- **ACCURETIC 10/12.5 mg:** Contains 10 mg of quinapril (as hydrochloride) and 12.5 mg of hydrochlorothiazide - pink, oval, biconvex, film-coated tablets with bisecting score on both sides and PD222 on one side.
- **ACCURETIC 20/12.5 mg:** Contains 20 mg of quinapril (as hydrochloride) and 12.5 mg of hydrochlorothiazide - pink, triangular, biconvex, film-coated tablets with bisecting score and PD220 on one side.
- **ACCURETIC 20/25 mg:** Contains 20 mg of quinapril (as hydrochloride) and 25 mg of hydrochlorothiazide - pink, round, biconvex, film-coated tablets with PD223 on one side.

Available in blisters of 28 and 30 tablets.

Composition

Medicinal Ingredients: ACCURETIC tablets contain quinapril (as hydrochloride) and hydrochlorothiazide in ratios of 10 mg: 12.5 mg; 20 mg: 12.5 mg and 20 mg: 25 mg, respectively.

Nonmedicinal Ingredients: Candelilla wax, crospovidone, lactose, magnesium carbonate, magnesium stearate, povidone, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

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 (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 14 NON-CLINICAL 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 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions).

Cardiovascular

Dual blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the Renin-Angiotensin System (RAS): There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as ACCURETIC, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including acute renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2). Therefore, the use of ACCURETIC in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including ACCURETIC, 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, acute renal failure, and hyperkalemia. Administration should be limited to individually defined cases with close monitoring of renal function and blood potassium levels (see 2 CONTRAINDICATIONS).

Hypotension

Symptomatic hypotension has occurred after administration of quinapril, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (See 8 ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ACCURETIC should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ACCURETIC is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be 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 supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. If symptoms persist, the dosage should be reduced, or the drug discontinued.

Valvular 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.

Endocrine and Metabolism

Initial and periodic determination of serum electrolytes should be performed at appropriate intervals to detect possible electrolyte imbalance.

Hyperkalemia/Hypokalemia

Quinapril: Elevated serum potassium (>5.7 mMol/L) was observed in approximately 2% of patients receiving quinapril. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in <0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia, potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs known to raise serum potassium levels (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Serum Electrolytes, 8 ADVERSE REACTIONS, and 9 DRUG INTERACTIONS, Agents Increasing Serum Potassium, Trimethoprim-containing products). The addition of a potassium-sparing diuretic to ACCURETIC, which contains a diuretic, is not recommended.

Hydrochlorothiazide: Treatment with thiazide diuretics has been associated with hypokalemia.

Hypokalemia can also sensitize or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH or with other drugs known to increase the risk of hypokalemia induced by thiazide diuretics (e.g. aminoglycoside antibiotics, cisplatin, foscarnet, amphotericin B and loop diuretics (furosemide)).

Quinapril/Hydrochlorothiazide: The opposite effects of hydrochlorothiazide and quinapril on serum potassium may approximately balance each other in many patients so that no net effect will be seen. In other patients, one or the other effect may be dominant.

Other electrolytes imbalances

Hydrochlorothiazide: In addition to hypokalemia, treatment with thiazide diuretics has also been associated with hyponatremia and hypochloremic alkalosis. These disturbances have sometimes been manifest as one or more of the following: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, confusion, seizures and vomiting.

Chloride deficits secondary to thiazide therapy are generally mild and require specific treatment only under extraordinary circumstances (e.g. in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients, especially in hot weather; appropriate therapy is water restriction rather than administration of salt, except when the hyponatremia is life threatening. In actual salt depletion, replacement of salt is the therapy of choice.

Thiazides may decrease 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 hypoparathyroidism. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland have been observed, with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been seen. Thiazides should be discontinued before performing tests for parathyroid function.

Thiazides increase the urinary excretion of magnesium, and hypomagnesaemia may result.

Hypoglycemia/Hyperglycemia and Diabetes

Quinapril: ACE inhibitors may reduce insulin resistance and may lead to hypoglycemia in diabetic *patients on insulin or oral hypoglycemic agents; closer monitoring of diabetic patients may be required.*

Hydrochlorothiazide: Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance. Monitor glycemic control, supplement potassium, if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required (see 9 DRUG INTERACTIONS, Antidiabetic agents (e.g. insulin, oral hypoglycemic agents, sitagliptin)).

Overt diabetes may be precipitated in susceptible individuals.

Other metabolic parameters

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

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

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Hematologic

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Agranulocytosis did occur during quinapril treatment in one patient with a history of neutropenia during previous captopril therapy. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Hepatic/Biliary/Pancreatic

Impairment of Liver Function

ACCURETIC should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Also, since the metabolism of quinapril to quinaprilat is normally dependent upon hepatic esterase, patients with impaired liver function could develop markedly elevated plasma levels of quinapril.

Elevations of liver enzymes and/or serum bilirubin have been reported for ACCURETIC (see 8

ADVERSE REACTIONS). There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ACCURETIC should be used with particular caution in patients with pre-existing liver abnormalities. A full set of liver function tests and any other necessary investigations should be obtained in these patients before administration of the drug and close monitoring of response and metabolic effects should apply. Discontinuation of ACCURETIC should be considered when appropriate.

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

Immune

Hypersensitivity to ACE inhibitor

Angioedema

Angioedema has been reported in patients treated with ACE inhibitors, including quinapril. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCURETIC (quinapril hydrochloride and hydrochlorothiazide) 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 the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy (including but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see 8 ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

Patients taking a concomitant mTOR inhibitor (e.g. temsirolimus), DPP-4 inhibitor (e.g. sitagliptin) or neutral endopeptidase (NEP) inhibitor may be at increased risk for angioedema. Caution should be used when either initiating ACE inhibitor therapy in patients already taking a mTOR inhibitor, DPP-4 inhibitor 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; 9 DRUG DRUG INTERACTIONS). ACCURETIC must not be initiated until at least 36 hours have elapsed following discontinuation of sacubitril/valsartan therapy. If treatment with ACCURETIC is stopped, sacubitril/valsartan therapy must not be initiated until 36 hours after the last dose of ACCURETIC.

Patients with a history of angioedema related or unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 2 CONTRAINDICATIONS).

Anaphylactoid Reactions during Membrane Exposure

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Anaphylactoid Reactions during LDL Apheresis

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

Anaphylactoid Reactions during Desensitization

There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge to an ACE inhibitor.

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 ACCURETIC (see 9 DRUG INTERACTIONS).

Hypersensitivity to Hydrochlorothiazide

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

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Monitoring and Laboratory Tests

Serum Electrolytes: Variations of serum electrolytes levels have been observed with ACCURETIC. Initial and periodic determination of serum electrolytes should be performed at appropriate intervals to detect possible electrolyte imbalance (See 2 CONTRAINDICATIONS and 7 WARNINGS and PRECAUTIONS).

Creatinine and Blood Nitrogen: Increases (>1.25x ULN) in serum creatinine and blood urea nitrogen (BUN) were observed in 3% and 4% respectively, of patients treated with ACCURETIC (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Hepatic: Elevations of liver enzymes and/or serum bilirubin have occurred in patients receiving ACCURETIC. If a patient receiving ACCURETIC experience any unexplained symptoms,

particularly during the first weeks or months of treatment, a full set of liver function tests and any other investigation should be carried out. Discontinuation of ACCURETIC should be considered when appropriate. In patients with pre-existing liver abnormalities, baseline liver function tests should be obtained before administration of the drug. The response and metabolic effects should be closely monitored (see 7 WARNINGS AND PRECAUTIONS).

Glucose: Elevations in glucose values have occurred. Monitor glycemic control, supplement potassium, if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia/Hyperglycemia and Diabetes and 9 DRUG INTERACTIONS, Antidiabetic agents (e.g. insulin, oral hypoglycemic agents, sitagliptin)).

Triglyceride: Elevations in triglyceride values have occurred (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Other metabolic parameters).

Serum Uric Acid: Elevations in serum uric acid values have occurred (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Other metabolic parameters).

Hematology: Possibly clinically important increases and decreases in hematology parameters have occurred. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Neutropenia/Agranulocytosis).

Other laboratory test values with clinically important deviations during controlled and uncontrolled trials included: Magnesium, Cholesterol, PBI, Parathyroid Function Tests and Calcium (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Other electrolytes imbalances and Other metabolic parameters).

Ophthalmologic

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma related to Hydrochlorothiazide

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, blurred vision 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/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, ACE inhibitors will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be

corrected by volume expansion.

Renal

Azotemia

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, ACCURETIC should be discontinued.

Renal Impairment

The use of ACE inhibitors, including ACCURETIC, with ARBs or aliskiren-containing drugs is contraindicated in patients with moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73m^2) (see 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS, Aliskiren-containing medicines and Angiotensin receptor blockers (ARBs)).

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 (see 8 ADVERSE REACTIONS and 4 DOSAGE ADMINISTRATION).

Use of ACCURETIC should be followed by the appropriate assessment of renal function (see 8 ADVERSE REACTIONS and 4 DOSAGE ADMINISTRATION).

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of ≤30 mL/min (i.e. moderate or severe renal insufficiency) (see 8 ADVERSE REACTIONS and 4 DOSAGE ADMINISTRATION).

Reproductive Health: Female and Male Potential

- **Fertility**

  See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women and 14 NON-CLINICAL TOXICOLOGY

- **Teratogenic Risk**

  See 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women and 14 NON-CLINICAL TOXICOLOGY

Respiratory

Cough

A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of quinapril has been reported. Such possibility should be considered as part of the differential diagnosis of the cough.

Acute Respiratory Distress Syndrome (ARDS)

Severe cases of acute respiratory toxicity, including ARDS have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, ACCURETIC (quinapril/hydrochlorothiazide) should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Sensitivity/Resistance

Due to the presence of lactose, patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency should not take ACCURETIC (see 2 CONTRAINDICATIONS).

Skin

Psoriasis and Aggravation of Psoriasis

Psoriasis or aggravation of psoriasis have been reported in patients receiving ACE inhibitors. ACCURETIC should be used with caution in patients, especially those with a medical history or family history of psoriasis. Consider discontinuation of ACCURETIC if clinically significant psoriasis or psoriasis aggravation occurs.

Photosensitivity

Photosensitivity reactions have been reported with the use of thiazide diuretics.

If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

7.1 Special Populations

7.1.1 Pregnant Women

Quinapril is contraindicated in pregnancy (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS). 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, ACCURETIC should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

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

Infants with a history of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

If oligohydramnios is observed, a non-stress test (NST), and/or a biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. If concerns regarding fetal well-being still persist, a contraction stress test (CST) should be considered. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Thiazides cross the placental barrier and appear in cord blood. Although studies in humans have not been done, effects to the fetus may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Animal Data: No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180x maximum daily human dose), despite maternal toxicity at 150 mg/kg/day. Offspring body weights were reduced in rats treated late in gestation and during lactation with doses of ≥25 mg/kg/day. Quinapril hydrochloride was not teratogenic in rabbits; however, maternal and embryo toxicity were seen in some rabbits at doses as low as 0.5 mg/kg/day and 1 mg/kg/day, respectively.

No adverse effects on fertility or reproduction were observed in rats at quinapril dose levels ≤100 mg/kg/day (60x maximum daily human dose).

7.1.2 Breast-feeding

The presence of concentrations of ACE inhibitor has been reported in human milk. Thiazides also appear in human milk. The use of ACCURETIC is contraindicated during breast-feeding (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Quinapril: Therapeutic effects appear to be the same for elderly (>65 years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

This information is not available for this drug product.

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.

ACCURETIC (quinapril hydrochloride and hydrochlorothiazide) was evaluated for safety in 1571 patients with essential hypertension, including 943 patients in controlled studies (see Table 3), 345 patients in placebo-controlled trials, and 517 patients who were treated with ACCURETIC for ≥1 year. Adverse reactions were limited to those reported previously with quinapril or hydrochlorothiazide (HCTZ) when used separately for the treatment of hypertension.

Serious or clinically significant adverse reactions observed in <0.2% of patients treated with quinapril and HCTZ were: hematemesis, gout, syncope and angioedema. Therapy was discontinued in 2.1% of patients due to an adverse event (AE). Headache (0.5%) and dizziness (0.3%) were the most frequent reasons for withdrawal.

The most frequent adverse experiences in controlled trials were headache (6.7%), dizziness (4.8%), cough (3.2%) and fatigue (2.9%). The cough is characteristically non-productive, persistent and resolves after discontinuation of therapy (see 7 WARNINGS AND PRECAUTIONS, Respiratory, Cough).

Table 3. Adverse Events in ≥1% of Quinapril/Hydrochlorothiazide Patients in Controlled Clinical Studies.

	Quinapril / HCTZ n = 943 (%)	Quinapril n = 799 (%)
Cardiac Disorders		
Vasodilatation	1.0	0.4
Gastrointestinal Disorders		
Dyspepsia	1.2	1.9
Nausea and/or vomiting	1.8	2.0
Diarrhea	1.4	1.7
Abdominal pain	1.7	1.6
General Disorders and Administration Site Conditions		
Asthenia	1.1	1.2
Fatigue	2.9	2.0
Headache	6.7	4.8
Back pain	1.5	0.7
Chest pain	1.0	1.2
Viral infection	1.9	2.0
Musculoskeletal and Connective Tissue Disorders		
Myalgia	2.4	0.9
Nervous System Disorders		
Dizziness	4.8	2.7
Insomnia	1.2	1.5
Somnolence	1.2	0.9
Vertigo	1.0	0.3

	Quinapril / HCTZ n = 943 (%)	Quinapril n = 799 (%)
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngitis	1.1	1.4
Rhinitis	2.0	3.0
Bronchitis	1.2	1.3
Coughing	3.2	2.7
Upper respiratory infection	1.3	1.1

8.3 Less Common Clinical Trial Adverse Reactions

Clinical AEs regardless of relationship to therapy, occurring in ≥0.5% to <1.0% of patients treated with quinapril plus HCTZ in controlled and uncontrolled trials and less frequent clinically significant events seen in clinical trials or in post marketing experience included:

Cardiac Disorders:	Hypotension, palpitations, tachycardia
Gastrointestinal Disorders:	Dry mouth or throat, flatulence, pancreatitis
Respiratory, Thoracic and Mediastinal Disorders:	Dyspnea, sinusitis
Psychiatric Disorders:	Nervousness, paresthesia
Skin and Subcutaneous Tissue Disorders	Alopecia, erythema multiforme, exfoliative dermatitis, pemphigus, pruritus, rash, psoriasis
Renal and Urinary Disorders	Urinary tract infection
Reproductive System and Breast Disorders	Impotence

Rare AEs, not listed above, which have been reported with either HCTZ, quinapril, or the combination include:

Blood and Lymphatic System Disorders	Agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, purpura, thrombocytopenia
Cardiac Disorders:	Atrial flutter, cerebrovascular accident, heart arrest, heart failure, myocardial ischemia, necrotizing angiitis, transient ischemic attack, vasodilation. Orthostatic hypotension may occur, especially in elderly patients with reduced plasma volume, and may be potentiated by alcohol, barbiturates, or narcotics

Congenital, Familial and Genetic Disorders	Fetal/neonatal injury including: anuria, hypotension, oligohydramnios, skull hypoplasia, reversible or irreversible renal failure, and death (See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women)
Ear and Labyrinth Disorders	Tinnitus
Eye Disorders	Acute myopia and acute angle closure glaucoma (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic, Acute myopia and acute angle closure glaucoma), transient blurred vision, xanthopsia
Gastrointestinal Disorders:	Anorexia, bloody stools, constipation, cramping, gastric irritation, GI hemorrhage, jaundice (intrahepatic cholestatic), pancreatitis, sialadenitis, taste disturbance
Respiratory, Thoracic and Mediastinal Disorders:	Respiratory distress including pneumonitis, asthma, hoarseness
Nervous System Disorders:	Amnesia, confusion, facial paralysis, paresthesias, polyneuritis
Psychiatric Disorders:	Anxiety
Renal and Urinary Disorders	Dysuria, glycosuria, hematuria, impaired renal function, polyuria
Other	Allergy, anaphylactic reactions, arthritis, chill, dehydration, face edema, fever, fracture, muscle spasm, restlessness, weakness, weight increase

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

This information is not available for this drug product.

8.5 Post-Market Adverse Reactions

Non-melanoma skin cancer:

Some pharmacoepidemiologic studies have suggested a higher risk of squamous cell carcinoma and basal cell carcinoma of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis undertaken by Health Canada suggested, with important uncertainty, 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 squamous cell carcinoma 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 basal cell carcinoma per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

Eye disorders:

Choroidal effusion, acute myopia, acute angle-closure glaucoma (frequency unknown).

Respiratory

Acute respiratory distress syndrome (ARDS) has been reported in very rare instances (see 7 WARNINGS 7 PRECAUTIONS, Respiratory).

9 DRUG INTERACTIONS

9.1 Serious drug interactions

Concomitant use with with sacubitril/valsartan is contraindicated due to an increased risk of angioedema (see 2 CONTRAINDICATIONS; 7 WARNINGS & PRECAUTIONS; 9.4 Drug-drug interactions.

9.2 Drug-Behavioural Interactions

Alcohol use should be avoided when taking ACCURETIC as it can cause orthostatic hypotension.

9.3 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/ Common name]	Source of Evidence	Effect	Clinical comment
Adrenergic neuron blocking agents (e.g. MAO inhibitors, chlorpromazine)	---		These agents affect sympathetic activity and should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to quinapril.

Potassium sparing diuretics (e.g. spirolactone, triamterene, amiloride), potassium supplements or drugs that raise serum potassium	---	Since quinapril decreases aldosterone production, elevation of serum potassium may occur.	Since ACCURETIC contains a diuretic, the addition of a potassium-sparing diuretic is not recommended. These drugs should be given with caution and with frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.
Alcohol, barbiturates or narcotics	C	Potentiation of orthostatic hypotension may occur in the presence of hydrochlorothiazide.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Aliskiren-containing medicines	CT	Dual blockade of the renin-angiotensin-aldosterone system by combining an ACE inhibitor with aliskiren-containing medicines is not recommended since there is an increased risk of hypotension, syncope, stroke, hyperkalemia and changes in renal function, including renal failure.	The use of ACCURETIC in combination with aliskiren-containing medicines is contraindicated in patients with • diabetes mellitus (type 1 or type 2), • moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2), • hyperkalemia (> 5mMol/L) or • congestive heart failure who are hypotensive. It is not recommended in other patients (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual blockade of the Renin-Angiotensin System (RAS))

Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Angiotensin receptor blockers (ARBs)	CT	Dual blockade of the renin-angiotensin-aldosterone system by combining an ACE inhibitor with ARBs is not recommended since there is an increased risk of hypotension, syncope, stroke, hyperkalemia and changes in renal function, including renal failure.	The use of ACCURETIC in combination with ARBs is contraindicated in patients with • diabetes mellitus (type 1 or type 2), • moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2), • hyperkalemia (> 5mMol/L) or • congestive heart failure who are hypotensive. It is not recommended in other patients (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual blockade of the Renin-Angiotensin System (RAS))
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 ACCURETIC 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose for thiazide, if necessary.

Antidiabetic agents (e.g. insulin oral hypoglycemic agents)	CT	ACE inhibitors may reduce insulin resistance and may lead to hypoglycemia in diabetic patients on insulin or oral hypoglycemic agents.	Closely monitor diabetic patients (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia and Diabetes).
		Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia and Diabetes).
Anti-neoplastic drugs e.g. cyclo-phosphamide, methotrexate	C, CT	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
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.

Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur when administered with hydrochlorothiazide	Monitor serum potassium, and adjust medications, as required.
Digoxin	CT	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 levels closely. Supplement potassium or adjust doses of digoxin or thiazides, as required.
DDP-IV inhibitors (linagliptin, saxagliptin, sitagliptin)		Patients taking concomitant DPP-4 inhibitor therapy may be at increased risk for angioedema.	Caution should be used when either initiating ACE inhibitor therapy in patients already taking a DPP-4 inhibitor or vice versa (see 7 WARNINGS AND PRECAUTIONS, General, Angioedema).
Anti-cholinergic agents, e.g. atropine; Prokinetic agents, e.g. meto-clopramide, 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 the thiazide component of ACCURETIC may be required.

Gold	C	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including ACCURETIC.	
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RC	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dose adjustment of gout medications may be required.
Lithium	CT	Thiazide diuretic agents and ACE inhibitors reduce the renal clearance of lithium and increase the risk of lithium toxicity.	Concomitant use of thiazide diuretics or ACE inhibitors with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely.
Neutral endopeptidase (NEP) inhibitor	---	ACE inhibitors are known to cause angioedema. This risk may be elevated when used concomitantly with a neutral endopeptidase inhibitor Patients taking concomitant neutral endopeptidase inhibitor may be at increased risk for angioedema.	Caution should be used when either initiating ACE inhibitor therapy in patients already taking a neutral endopeptidase inhibitor or vice versa (see 7 WARNINGS AND PRECAUTIONS, General, Angioedema).

Non-Steroidal Anti Inflammatory Drugs (NSAID) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors)	CT	There are two types of interaction between ACCURETIC and NSAIDs: Interaction with ACE-Inhibitor component of ACCURETIC: In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including quinapril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. The antihypertensive effect of ACE inhibitors, including quinapril, may be attenuated by NSAIDs. Interaction with Diuretic component of ACCURETIC: In some patients, the administration of a NSAID agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. NSAID-induced inhibition of renal prostaglandins leading to decreases of	If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustment may be required.

		renal blood flow, along with thiazide-induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk.	
Other Anti-hypertensive Agents	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACEI, ARB, ARB, and direct renin inhibitors)	
Pressor Amines (e.g. noradrenaline)	---	Possible decreased response to pressor amines may occur in the presence of a thiazide diuretic but is not sufficient to preclude their use.	
sacubitril/ valsartan (e.g. ENTRESTO™)		Increased risk of angioedema	ACCURETIC must not be initiated until at least 36 hours have elapsed following discontinuation of sacubitril/valsartan therapy. If treatment with ACCURETIC is stopped, sacubitril/valsartan therapy must not be initiated until 36 hours after the last dose of ACCURETIC. (See 2 CONTRAINDICATIONS)
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.

mTOR inhibitors e.g. sirolimus, everolimus, temsirolimus	CT	An increased incidence of angioedema was observed in patients taking ACE inhibitors and mTOR inhibitors (mammalian target of rapamycin inhibitors)	Caution should be used when either initiating ACE inhibitor therapy in patients already taking mTOR inhibitors or vice versa (see 7 WARNINGS AND PRECAUTIONS, General, Angioedema).
Skeletal muscle relaxants of the curare family, e.g., tubocurare	C	Thiazide drugs may increase responsiveness of some skeletal muscle relaxants, such as curare derivatives.	
Tetracycline	---	Concomitant administration of tetracycline with quinapril reduced the absorption of tetracycline in healthy volunteers (by 28-37%) due to the presence of magnesium carbonate as an excipient in the formulation.	This interaction should be considered with concomitant use of ACCURETIC and tetracycline or other drugs which interact with magnesium.
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels. Use potassium supplements or adjust topiramate dose as necessary.
Trimethoprim-containing products (sulfamethoxazole/ trimethoprim)	C	In patients who are elderly or have compromised renal function, co-administration of an ACE inhibitor with sulfamethoxazole/trimethoprim has been associated with severe hyperkalemia, likely due to the hyperkalemic effects of trimethoprim.	ACCURETIC and trimethoprim-containing products should only be co-administered with caution and with appropriate monitoring of serum potassium.

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

9.4 Drug-Food Interactions
The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when administered during a high-fat meal. However, no effect on quinapril absorption occurs when taken during a regular meal.

9.5 Drug-Herb Interactions
Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions
Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action
ACCURETIC (quinapril hydrochloride and hydrochlorothiazide) is a fixed-combination tablet which combines the antihypertensive actions of an angiotensin-converting enzyme (ACE) inhibitor, quinapril hydrochloride and a diuretic, hydrochlorothiazide (HCTZ). In clinical studies, administration of this combination produced greater reductions in blood pressure (BP) than the single agents given alone.

Quinapril:

In human subjects, quinapril at single oral doses of 10-20 mg/day produced 95-100% inhibition of plasma ACE activity at 0.5 hour postdose, with >80% inhibition persisting at 24 hours postdose. Multiple oral doses of quinapril to humans for 12-weeks (20-80 mg/day) confirmed the inhibitory effect on plasma ACE and showed that it produces corresponding decreases in angiotensin II with significant increases in plasma renin activity. Once or 2x daily dosing did not alter the results.

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.

10.2 Pharmacodynamics
Quinapril:

Quinapril is a nonpeptide, nonsulphydryl ACE inhibitor. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor angiotensin II. After absorption, quinapril is rapidly de-esterified to quinaprilat (quinapril diacid), its principal active metabolite. Its primary mode of action is to inhibit circulating and tissue ACE, thereby decreasing vasopressor activity and aldosterone secretion. Although the decrease in aldosterone is small, it results in a small increase in serum K^+ (see 7 WARNINGS AND PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

ACE is identical to kininase II. Thus, quinapril may interfere with the degradation of bradykinin, a potent peptide vasodilator. However, it is not known whether this system contributes to the therapeutic effects of quinapril.

In animal studies, the antihypertensive effect of quinapril outlasts its inhibitory effect on circulating ACE. Tissue ACE inhibition more closely correlates with the duration of antihypertensive effects and this may be related to enzyme binding characteristics.

Administration of 10-40 mg of quinapril to patients with essential hypertension results in a reduction of both sitting and standing BP with minimal effect on heart rate. Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2-4 hours after dosing. Achievement of maximum BP lowering effects may require 2-4 weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained throughout the 24-hour dosing interval in most patients. While the dose response relationship is relatively flat, a dose of 40 mg was somewhat more effective at trough than 10-20 mg, and 2x daily dosing tended to give a somewhat lower BP than 1x daily dosing with the same total daily dose. The antihypertensive effect of quinapril was maintained during long-term therapy with no evidence of loss of effectiveness.

Hemodynamic assessments in patients with essential hypertension indicate that BP reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate and cardiac index. There was an increase in renal blood flow which was not significant. Little or no change in glomerular filtration rate (GFR) or filtration fraction was observed.

Hydrochlorothiazide:

HCTZ acts directly on the kidney to increase excretion of sodium and chloride, and an accompanying volume of water. HCTZ also increases the excretion of potassium and bicarbonate and decreases calcium excretion.

As a result of its diuretic effect, HCTZ increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases urinary potassium loss. Administration of quinapril inhibits the renin-angiotensin-aldosterone axis and tends to attenuate the potassium decrease associated with HCTZ.

The mechanism underlying the antihypertensive activity of diuretics is unknown. During chronic administration peripheral vascular resistance is reduced; however, this may be secondary to changes in sodium balance.

Quinapril/Hydrochlorothiazide:

When quinapril and HCTZ are given together, the antihypertensive effects are approximately additive.

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10.3 Pharmacokinetics

Quinapril:

Absorption:
Following oral administration of quinapril, peak plasma concentrations of quinapril occur within 1 hour. Based on the recovery of quinapril and its metabolites in urine, the extent of absorption is ≥60%.

Distribution:
Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

Metabolism:
Following absorption, quinapril is de-esterified to its major active metabolite, quinaprilat (quinapril diacid), a potent ACE inhibitor, and to minor inactive metabolites. Quinapril has an apparent half-life in plasma of approximately 1 hour. Peak plasma quinaprilat concentrations occur approximately 2 hours after an oral dose of quinapril.

Elimination:
Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of approximately 3 hours. Quinaprilat has an elimination half-life in plasma of approximately 2 hours with a prolonged terminal phase of 25 hours.

The rate and extent of quinapril absorption are diminished moderately (approximately 25-30%) when administered during a high-fat meal. However, no effect on quinapril absorption occurs when taken during a regular meal.

Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

Hydrochlorothiazide:

Absorption:
After oral administration of HCTZ, diuresis begins within 2 hours, peaks in about 4 hours, and lasts about 6-12 hours; the extent of absorption is approximately 50-80%.

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.

Elimination:
HCTZ is excreted unchanged by the kidney. When plasma levels have been followed for ≥24 hours, the plasma half-life has been observed to vary between 4-15 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. HCTZ crosses the placental but not the blood-brain barrier.

Quinapril/Hydrochlorothiazide:

Concomitant administration of quinapril and HCTZ has little or no effect on the bioavailability or the pharmacokinetics of either drug.

Special Populations and Conditions

- **Geriatrics**

  Quinapril: Therapeutic effects appear to be the same for elderly (>65 years of age) and younger adult patients given the same daily dosages, with no increase in AEs in elderly patients.

- **Ethnic Origin**

  Quinapril: The antihypertensive effect of ACE inhibitors is generally lower in black than in non-black patients.

- **Renal Insufficiency**:

  Quinapril: The disposition of quinapril and quinaprilat in patients with renal insufficiency is similar to that in patients with normal renal function until creatinine clearance is ≤60 mL/min. With creatinine clearance <60 mL/min, peak and trough quinaprilat concentrations increase, apparent half-life increases, and time to steady state may be delayed. The elimination of quinaprilat may be reduced in elderly patients (>65 years) and in those with heart failure; this reduction is attributable to decrease in renal function (see 4 DOSAGE and ADMINISTRATION). Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril.

  Pharmacokinetic studies in patients with end-stage renal disease or chronic hemodialysis or continuous ambulatory peritoneal dialysis indicate that dialysis has little effect on the elimination of quinapril and quinaprilat.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature 15-25°. Dispense in well-closed containers.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

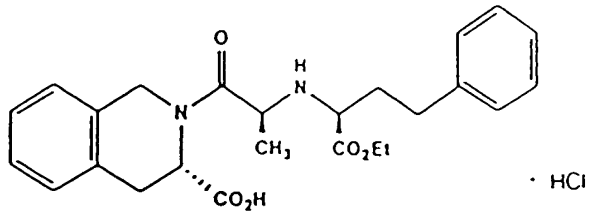
Proper name: Quinapril (as Hydrochloride) and Hydrochlorothiazide

Quinapril Hydrochloride

Chemical name: [3S-[2[R*(R*)],3R*]] 2-[2-[[1-(ethoxycarbonyl)-3- phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid monohydrochloride

Molecular formula $C_{25}H_{30}N_2O_5.HCl$ (M.W. = 474.98)

Molecular Structure



Description Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents. The pH of a 1% solution in distilled water is 2.5.

Dissociation Constants pK_{a1} = 2.8

pK_{a2} = 5.4

Melting Range Melts with decomposition, 108-115°C

Solubility

Solvent	Solubility (mg/mL)
Distilled water (pH 7.4 and 7.0)	>100
0.1 N hydrochloric acid	>100
0.05 M acetate buffer, pH 4.0	6.9
0.05 M phosphate buffer, pH 7.0	>100
0.05 M phosphate buffer, pH 7.4	>100
Methanol	>50
Ethanol (95%)	>50
Acetone	>50
Chloroform	>50
Polyethylene glycol 400	>100

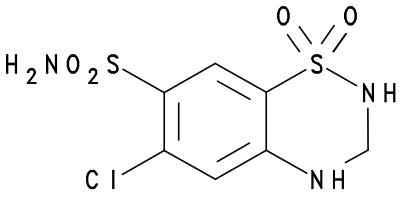
	Polyethylene glycol	>100
Partition Coefficient (Octanol-Water)	Aqueous Buffer	Log-P
	0.1N hydrochloric acid	0.86
	0.05M phosphate buffer, pH 2.5	0.68
	0.05M phosphate buffer, pH 4.0	1.35
	0.05M phosphate buffer, pH 7.4	0.33

Hydrochlorothiazide

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

Molecular formula $C_7H_8ClN_3O_4S_2$ (M.W. = 297.72)

Molecular Structure



Description Hydrochlorothiazide is a white to off-white, crystalline powder which is practically insoluble in water, but freely soluble in sodium hydroxide solution.

Dissociation Constants pK_{a1} = 7.0

pK_{a2} = 9.2

Melting Range 273-275°C

Solubility	Solvent	Solubility (mg/mL)
	Water pH 6.2	60.9×10^{-3}
	Water pH 7.2	108×10^{-3}
	0.9% NaCl	59.4×10^{-3}
	0.1 N hydrochloric acid	60.8×10^{-3}
	0.1 N acetic acid	63.6×10^{-3}
	0.1 N acetic buffer, pH 4.4	62.3×10^{-3}
	0.067 M phosphate buffer, pH 7.4	61.6×10^{-3}
	0.05 M borate buffer	103×10^{-3}
	1 M ammonia (25)	2.2
	0.1 N NaOH	1.79
	Simulated gastric fluid pH 1.1	108×10^{-3}

	Simulated intestinal fluid pH 7.4	109 x 10^{-3}
	Acetone	13.7
	Acetic acid	0.15
	Acetonitrile	2.0
	Ethylacetate	0.59
	Chloroform	0.1
	Ethanol (96%)	1.3 - 1.4
	Methanol	3.9 - 4.1
	Dichloromethane	<0.02
Partition Coefficient (Octanol-Water)	Aqueous Buffer	Log-P
	0.1 N Hydrochloric acid	1.94
	0.1 M glycine buffer, pH 3.0	0.866
	0.067 M phosphate buffer, pH 7.4	0.855

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Two controlled studies evaluated the efficacy and safety of quinapril and HCTZ combination therapy compared with each drug given as monotherapy in patients with essential hypertension. The combination therapy caused a statistically significant greater fall in diastolic blood pressure (DBP) than each drug given as monotherapy. In a placebo controlled study, when quinapril hydrochloride (10 mg, 40 mg) and HCTZ (12.5 mg, 25 mg) were administered alone or in combination, mean reductions in DBP (at trough) produced by quinapril monotherapy ranged from 7.3-10.3 mmHg, by HCTZ monotherapy from 7.2- 11.4 mmHg, and by combination therapy from 8.2-14.9 mmHg. Placebo produced a mean reduction in DBP of 2.2 mmHg.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The results of quinapril toxicity from chronic, carcinogenicity. genotoxicity, reproductive studies are given in Tables, 5-8 respectively.

Table 9 summarizes the results of toxicity studies with quinaprilat, the major active metabolite of quinapril.

Table 5: Chronic Toxicity Studies of Quinapril

Species	Duration (Week)	No. of Animals/ Sex/Group	Route	Doses (mg/kg/day)	Results
Rat	57o	30	PO	UC[2], VC[2], 10, 50, 100	No drug-related deaths; transient post-dose salivation, body weight gain suppression, increased BUN, decreased glucose, increased plasma renin level, decreased heart weight, JGA hypertrophy and hyperplasia with increased granules; degenerative changes in kidneys.
Dog	52	4	PO	VC, 10, 50, 100	No deaths; elevation of plasma renin and liver enzyme levels, focal areas of chronic active inflammation in the liver at 100 mg/kg; gastric erosion at 50 mg/kg, and hypertrophy/hyperplasia of renal JGA.

[1] 52 weeks treatment plus 4 weeks without treatment for some animals

[2] UC = Untreated Control; VC = Vehicle Control; BUN = blood urea nitrogen; JGA = juxtaglomerular apparatus.

Table 6: Reproductive Toxicology Studies of Quinapril

Species	No. of Animals/ Sex/Group	Route	Doses (mg/kg/day)	Duration of Dosing	Results
Fertility:					
Rat	12 Male 24 Female	PO	VC[1], 10, 50, 100	Males-60 days prior to mating Females-14 days prior to mating until weaning of offspring	No effects on fertility, no adverse effects on F_1 offspring parameters, and no teratogenic effects.
Teratology:					
Rat	5 Female	PO	100, 200, 400, 600, 800	Days 6 to 15 of gestation	No teratogenicity. Maternal deaths at 600 and 800 mg/kg; decreased fetal body weights at ≥200 mg/kg.
Rat	20 Female	PO	Uco, VC, 50, 150, 300	Days 6 to 15 of gestation	No fetotoxic or teratogenic effects. Reversible maternal toxicity.
Rabbit	5-7 Female	PO	10, 15, 25, 50, 100, 200, 400	Days 6 to 18 of gestation	Severe materno- and fetotoxicity.
Rabbit	5 Female	PO	VC, 1, 2, 4, 6, 8	Days 6 to 18 of gestation	Abortions and maternal deaths at 4, 6, and 8 mg/kg; materno- and fetotoxicity at doses >1 mg/kg.
Rabbit	14 Female	PO	VC 0.5, 1.0, 1.5	Days 6 to 18 of gestation	Not teratogenic. Maternal weight loss; increased incidence of postimplantation loss (embryotoxicity) at 1.0 and 1.5 mg/kg.
Perinatal/Postnatal:					

Rat	20 Female	PO	VC, 25, 75, 150	Day 15 of gestation to Day 20 of lactation	Reduction in offspring body weights from birth to Day 21 postnatally at 25, 75, and 150 mg/kg.

[1] UC = Untreated Control; VC = Vehicle Control

Table 7: Genetic Toxicology Studies of Quinapril

Test		Dosage Range	Results
Mutagenicity			
1) In Vitro	a) Initial cytotoxicity in *Salmonella* strain	≤10,000 µg/plate	Non-cytotoxic.
	b) Mutagenesis assay in *Salmonella*	625- 10,000 µg/plate	Negative-with or without metabolic activation.
	Mutagenesis assay in *Salmonella*		
2) In Vitro	a) Initial cytotoxicity assay	≤44,300 µg/mL	Cytotoxic at ≥1400 µg/mL.
	b) Point mutation assay in Chinese hamster lung cells	175- 1400 µg/mL	Negative - did not manifest direct acting or promutagen activity.
Cytogenetics			
1) In Vitro	a) Initial cytotoxicity assay	≤44,300 µg/mL	Cytotoxic at concentrations >700 µg/mL.
	b) Sister chromatid exchange (SCE) assay in Chinese hamster ovary cells	10.94- 1400 µg/mL	No increase in SCE at toxicity-limited doses ≤700 µg/mL in the presence of metabolic activation or ≤1400 µg/mL in the absence of metabolic activation.
2) In Vitro	a) Initial cytotoxicity assay	≤2700 µg/mL	Cytotoxic at ≥1200 µg/mL.
	b) structural chromosomal aberration (SCA) assay in Chinese hamster lung cells	800- 1800 µg/mL	Slight, statistically significant increase in SCA with metabolic activation; not considered biologically significant.
3) In Vivo	a) Mouse micronucleus assay	1- 1430 µg/kg	Not clastogenic; no increased frequency of micronuclei.

Table 8: Carcinogenicity Studies of Quinapril

Species	Duration (Week)	No. of Animals/ Sex/Group	Route	Doses(mg/kg/day)	Results
Mouse	104	50	PO	UC[1], VC[1], 5, 35, 75	No evidence of tumorigenic potential. Reduced heart weight, nephritis, and JGA hypertrophy/hyperplasia.
Rat	104	65	PO	UC, VC, 10, 50, 100	No evidence of tumorigenic potential. Reduced RBC, JGA hypertrophy/hyperplasia and renal degenerative changes.

[1]UC = Untreated Control; VC= Vehicle Control; JGA = juxtaglomerular apparatus; RBC = red blood cell count

Table 9: Toxicity Studies of Quinaprilat

Species	Duration (Week)	No. of Animals/ Sex/Group	Route	Doses(mg/kg/day)	Results
A. Acute Studies:					
Mouse	Single-dose	10	IV	VC[1], 250, 500, 1000	No deaths; MLD >1000 mg/kg. No clinical or gross pathological changes.
Rat	Single-dose	10	IV	VC, 50, 100, 200, 300, 400	No deaths; MLD >400 mg/kg. No clinical or gross pathological changes.
Dog	Escalating doses	1	IV	Escalating; 1-240	No deaths; MLD >240 mg/kg. Reduced food consumption, weight loss, and slight increase in myeloid to erythroid ratio.
B. Subacute Studies:					
Rat	2	5	IV	VC, 25, 50, 100, 200	No deaths, clinical signs or adverse pathological findings.
Rat	4	10	IV	VC, 20, 100, 200	No drug-related deaths or clinical signs; reduced heart weights.
Dog	2	1	IV	VC, 10, 50, 100	Sporadic increases in heart rate.
Dog	4	3	IV	VC, 10, 50, 100	No clinical or gross pathologic findings; JGA hypertrophy/hyperplasia.

[1] VC = Vehicle Control; MLD = median lethol dose; JGA = juxtaglomerular apparatus

C. Genotoxicity Studies:		
Test	**Dose range**	**Results**
Mutagenicity:		

In Vitro	a) Initial cytotoxicity in *Salmonella*	≤1200 µg/plate	Non-cytotoxic.
	b) Mutagenesis assay in *Salmonella*	75- 1200 µg/plate	Negative-with or without metabolic activation.

Quinapril Hydrochloride and Hydrochlorothiazide

The 14-day Median Lethal Dose (MLD) in mice was 1068/667 mg/kg quinapril/ HCTZ; in rats it was 4640/2896 mg/kg. For quinapril alone, the oral MLD ranged from 1440-2150 mg/kg for mice, and from 3531-4280 mg/kg in rats. In dogs, no drug-related clinical signs of toxicity were observed at doses of 125-250x the maximum human dose of quinapril given in combination with HCTZ, and 60-120x the maximum human dose of HCTZ in combination (100/60 mg/kg in males, 200/120 mg/kg in females).

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 pheochromocytoma 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ACCURETIC

Quinapril (as hydrochloride) and hydrochlorothiazide tablets

Read this carefully before you start taking **ACCURETIC** 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 **ACCURETIC.**

Serious Warnings and Precautions- Pregnancy

ACCURETIC should not be used during pregnancy. Taking **ACCURETIC** can cause injury or even death to your baby. If you discover that you are pregnant while taking ACCURETIC, stop the medication and contact your healthcare professional as soon as possible.

What is ACCURETIC used for?

ACCURETIC lowers high blood pressure.

How does ACCURETIC work?

ACCURETIC contains a combination of 2 drugs, quinapril hydrochloride and hydrochlorothiazide:

- Quinapril hydrochloride is an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in "PRIL". It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. This lowers blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking ACCURETIC regularly even if you feel fine.

What are the ingredients in ACCURETIC?

Medicinal ingredients: Quinapril hydrochloride and hydrochlorothiazide

Non-medicinal ingredients: Candelilla wax, crospovidone, lactose, magnesium carbonate, magnesium stearate, povidone, synthetic red iron oxide, synthetic yellow iron oxide and titanium oxide.

ACCURETIC comes in the following dosage forms:

Tablets:
10 mg quinapril hydrochloride and 12.5 mg hydrochlorothiazide
20 mg quinapril hydrochloride and 12.5 mg hydrochlorothiazide
20 mg quinapril hydrochloride and 25 mg hydrochlorothiazide

Do not use ACCURETIC if:

Do not take ACCURETIC if you:

- Are allergic to quinapril hydrochloride or hydrochlorothiazide or to any non-medicinal ingredients in the formulation
- Have a condition causing your body's immune system to attack your own tissues (collagen vascular disease)
- Are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in "-MIDE"
- Have experienced an allergic reaction (angioedema) with swelling of the hands, feet, or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing, to any ACE inhibitor or without a known cause. Be sure to tell your healthcare professional that this has happened to you
- Have been diagnosed with hereditary angioedema: an increased risk of getting an allergic reaction that is passed down through families. This can be triggered by different factors, such as surgery, flu, or dental procedures
- Are taking Entresto (sacubitril/valsartan), due to the increased risk of serious allergic reaction which causes swelling of the face or throat (angioedema) when taken with ACCURETIC.
- Have difficulty urinating or produce no urine
- Are pregnant or intend to become pregnant. Taking ACCURETIC during pregnancy can cause injury and even death to your baby
- Are breastfeeding. ACCURETIC passes into breast milk.
- Are taking aliskiren-containing medicines, such as Rasilez, **and** have one of the following conditions:
  - Diabetes
  - Kidney disease
  - High levels of potassium
  - Congestive heart failure combined with hypotension
- Are taking an angiotensin receptor blocker (ARB), another medicine to treat your high blood pressure, **and** have one of the following conditions:
  - Diabetes with end organ damage
  - Kidney disease
  - High levels of potassium
  - Congestive heart failure combined with hypotension.

You can recognize ARBs because their medicinal ingredient ends in "-**SARTAN**".

- Have one of the following rare hereditary diseases:
  - Galactose intolerance

- Lapp lactase deficiency
- Glucose-galactose malabsorption

Because lactose is a non-medicinal ingredient in ACCURETIC.

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

- Are allergic to any drug used to lower blood pressure or penicillin
- Have a condition causing your body's immune system to attack your own tissues (collagen vascular disease)
- Have recently received or are planning to get allergy shots for bee or wasp stings
- Have narrowing of an artery or a heart valve
- Have had a heart attack or stroke
- Have heart failure
- Have diabetes, liver or kidney problems
- Have lupus or gout
- Are on dialysis or receiving LDL apheresis (treatment to remove "bad cholesterol" from the blood)
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill")
- Are taking an antibiotic containing trimethoprim
- Are on a low-salt diet
- Are receiving gold (sodium aurothiomalate) injections
- Are less than 18 years old
- Are taking a neutral endopeptidase inhibitor. The combination with ACCURETIC is not recommended.
- Are taking an aliskiren-containing medicine, such as Rasilez, used to lower high blood pressure. The combination with ACCURETIC is not recommended.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN"
- Are taking a medicine that contains aliskiren, such as Rasilez, or an angiotensin receptor blocker (ARB). The combination with ACCURETIC is not recommended.
- Are currently taking anti-cancer (temsirolimus, everolimus), anti-rejection (sirolimus) or anti-diabetic (gliptins) drugs. Use of ACE inhibitors, such as ACCURETIC, with these drugs may increase the chance of having an allergic reaction.
- Have had skin cancer or have a family history of skin cancer.
- Have a greater chance of developing skin cancer because you have light-coloured skin, get sunburned easily, or are taking drugs to suppress your immune system.
- Have a medical history or family history of psoriasis (rash with itchy, scaly patches usually on the knees, elbows, trunk and scalp).
- Have had breathing or lung problems (including inflammation or fluid in the lungs) in the past following the use of medication containing hydrochlorothiazide. If you

experience any severe shortness of breath or difficulty breathing after taking ACCURETIC, stop the medication and seek medical attention immediately.

Other warnings you should know about:

Risk of skin cancer:

- ACCURETIC contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing non-melanoma skin cancer. The risk is higher if you have been taking ACCURETIC for many years (more than 3) or at a high dose.
- While taking ACCURETIC:
  - Make sure to regularly check your skin for any new lesions. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
  - Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.
  - Talk to your healthcare professional immediately if you get more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) during the treatment

Hydrochlorothiazide in ACCURETIC can cause sudden eye disorders:

- **Choroidal effusion**: an abnormal buildup of liquid behind the white outer layer of your eye that may result in vision changes.
- **Myopia:** sudden nearsightedness or blurred vision
- **Glaucoma:** an increased pressure in your eye, eye pain. Untreated, it may lead to permanent vision loss

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

You may become sensitive to the sun while taking ACCURETIC. Exposure to sunlight should be minimized until you know how you respond.

If you are going to have surgery and will be given an anesthetic. Be sure to tell your healthcare professional or dentist that you are taking ACCURETIC.

Driving and using machines: before you perform tasks, which may require special attention, wait until you know how you respond to ACCURETIC. Dizziness, light-headedness, or fainting can especially occur after the first dose and when the dose is increased. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hydrochlorothiazide in ACCURETIC can cause sudden respiratory toxicity, called Acute Respiratory Distress Syndrome (ARDS)

- Treatment with hydrochlorothiazide can lead to pulmonary edema, accumulation of fluid in lungs, within minutes to hours after taking the medicine.
- Talk to your healthcare professional immediately if you experience sudden onset in difficulty or labored breathing, fever, and low blood pressure (e.g. dizziness or light-headiness). Stop taking ACCURETIC and seek immediate medical help.

Development or worsening symptoms of psoriasis:
ACCURETIC can cause or worsen psoriasis. Speak to your healthcare professional if you experience symptoms of psoriasis or worsening psoriasis.

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 ACCURETIC:

- Adrenocorticotropic hormone (ACTH) used to treat West Syndrome
- Alcohol, narcotics (strong pain medications) or barbiturates (sleeping pills). They may cause low blood pressure and dizziness when you go from lying down or sitting to standing up.
- Amphotericin B, an antifungal drug
- Anti-cancer drugs, including cyclophosphamide, methotrexate, temsirolimus and everolimus
- Anti-rejection drugs, such as sirolimus (Rapamune)
- Antidepressants, in particular monoamine oxidase inhibitors (MAOI) or selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline
- Anti-diabetic drugs including insulin and oral medicines (e.g. metformin, gliptins, sulfonylureas)
- Bile acid resins used to lower cholesterol
- Calcium or vitamin D supplements
- Corticosteroids used to treat joint pain and swelling
- Chronic heart failure drugs such as Entresto (sacubitril / valsartan)
- Digoxin, a heart medication
- Drugs known to increase the potassium level in the blood such as a salt substitute that contains potassium, potassium supplements, potassium-sparing diuretic (a specific kind of "water pill") (e.g. spironolactone, triamterene, amiloride, sulfamethoxazole/trimethoprim).
- Drugs that slow down or speed up bowel function, including atropine, metoclopramide, and domperidone
- Drugs used to treat epilepsy, including carbamazepine and topiramate
- Drugs that lower blood sugar such as DDP-IV inhibitors (linagliptin, saxagliptin, sitagliptin).
- Gold for the treatment of rheumatoid arthritis
- Gout medications, including allopurinol and probenecid
- Lithium used to treat bipolar disease
- Neutral endopeptidase (NEP) inhibitors used to treat heart failure

- Non-steroidal anti-inflammatory drugs (NSAIDs) used to reduce pain and swelling. Examples include ibuprofen, naproxen, and celecoxib
- Blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), angiotensin receptor blockers (ARBs).
- Pressor amines (drugs which increase blood pressure, such as adrenaline)
- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurare
- Tetracycline (a type of antibiotic)

How to take Accuretic:

ACCURETIC is not for initial therapy. You must first be stabilized on the individual medicinal ingredients (quinapril hydrochloride and hydrochlorothiazide) of ACCURETIC. If your dosage matches the dosages in ACCURETIC, your healthcare professional may prescribe ACCURETIC taken once a day (instead of each medicinal ingredient as a separate pill).

Take ACCURETIC exactly as prescribed. It is recommended to take your dose at about the same time every day.

ACCURETIC can be taken with or without food.

If ACCURETIC causes upset stomach, take it with food or milk.

Usual adult dose:

The recommended starting dose is one 10 mg/12.5 mg tablet daily

Overdose:

If you think you, or a person you are caring for, have taken too much ACCURETIC, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, take it as soon as you remember. If it is almost time for the next dose, the missed dose should be skipped. You carry on with the next dose at the usual time. Do NOT double dose.

What are possible side effects from using ACCURETIC?

These are not all the possible side effects you may have when taking ACCURETIC. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Dizziness, headache, trouble sleeping
- Drowsiness, fatigue, weakness
- Cough
- Rash, itching
- Abdominal pain, upset stomach, decreased appetite, constipation,

- Muscle pain, spasms, back pain, restlessness
- Pins and needles in your fingers
- Nausea, vomiting, diarrhea
- Sore throat
- Stuffy, runny nose
- Reduced libido

ACCURETIC can cause abnormal blood test results. Your healthcare professional will decide when to perform blood test and will interpret the results.

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Low blood pressure: dizziness, fainting, light-headedness May occur when you go from lying or sitting to standing up	✓		
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		✓	
Non-melanoma skin cancer: lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly.		✓	
UNCOMMON			
Allergic reaction including; angioedema rash, hives. Swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Kidney disorder: decreased urination, nausea, vomiting, swelling of extremities, fatigue		✓	
Liver disorder: yellowing of the skin or eyes, dark urine,		✓	

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
abdominal pain, nausea, vomiting, loss of appetite			
Increased blood sugar: frequent urination, thirst, and hunger	✓		
Electrolyte imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		✓	
Fever		✓	
Shortness of breath			✓
Rash, red patches on skin, including psoriasis	✓		
RARE			
Decreased platelets: bruising, bleeding, fatigue, and weakness		✓	
Decreased white blood cells: infections, fatigue, fever, aches, pains and flu-like symptoms		✓	
Edema: Swelling of the hands, ankles or feet		✓	
Vomiting blood			✓
High nitrogen compound found in blood (Azotemia): rapid heart rate, high blood pressure, fatigue, confusion, light-headedness, dizziness, decreased urine production			✓
Chest Pain **Heart attack**			✓

VERY RARE			
Toxic epidermal necrolysis: severe skin peeling, especially in the mouth and eyes			✓
Acute Respiratory Distress Syndrome (ARDS): (inflammation of lung tissue or excess fluid in the lungs): Severe difficulty breathing, including shortness of breath. fever, weakness, and confusion.			
UNKNOWN			
Eye disorders: **Choroidal effusion:** blind spots, eye pain, blurred vision **Myopia:** sudden near sightedness or blurred vision **Glaucoma:** Increased pressure in your eyes, eye pain			✓
Anemia: fatigue, loss of energy, weakness, shortness of breath		✓	
Inflammation of the pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	
Tachycardia: Fast heart beats		✓	

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 ACCURETIC at room temperature, between 15° and 25°C. Protect from moisture. Keep in well closed container.

Keep out of reach and sight of children.

If you want more information about ACCURETIC:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp; the manufacturer's website http://www.pfizer.ca., or by calling 1-800-463-6001

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