Product Monograph

Including Patient Medication Information

[Pr]BENAZEPRIL

Benazepril Hydrochloride

Tablet

For oral use

5 mg, 10 mg and 20 mg of benazepril hydrochloride

House Standard

Angiotensin Converting Enzyme Inhibitor

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Recent Major Label Changes

3 Serious Warnings and Precautions Box	2025-06
7 Warnings and Precautions, Endocrine and Metabolism	2025-06
7 Warnings and Precautions, Hepatic/Biliary/Pancreatic	2025-06
7 Warnings and Precautions, Immune	2025-06
7 Warnings and Precautions, 7.1.1 Pregnancy	2025-06

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Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. Indications

BENAZEPRIL (benazepril hydrochloride tablets) is indicated for:

- Treatment of mild to moderate essential hypertension. It may be used alone or in association with thiazide diuretics.

The safety and efficacy of benazepril hydrochloride tablets in congestive heart failure and renovascular hypertension have not been established and therefore, its use in these conditions is not recommended.

The safety and efficacy of concurrent use of benazepril hydrochloride tablets with antihypertensive agents other than thiazide diuretics have not been established.

1.1. Pediatrics

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

Geriatrics (> 65 years of age): Although clinical experience has not identified differences in response between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out.

2. Contraindications

BENAZEPRIL 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 with or without previous treatment with an ACE inhibitor.
- Pregnant and breast-feeding women (See 7.1.1 Pregnancy and 7.1.2 Breastfeeding).
- Concomitant use of ACE inhibitors – including BENAZEPRIL – with a neprilysin inhibitor (e.g., sacubitril). BENAZEPRIL must not be administered within 36 hours of switching to or from a neprilysin inhibitor (eg. sacubitril/valsartan) (See 7 Warnings and Precautions, Immune, Angioedema and 9.4 Drug-Drug Interactions, Drugs causing angioedema).
- Concomitant use of angiotensin-converting-enzyme inhibitors (ACEIs) - including BENAZEPRIL - or of angiotensin receptor antagonists (ARBs) with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60 mL/min/1.73m^2). See 7 Warnings and Precautions, General, Dual Blockade of the

Renin-Angiotensin System (RAS); Renal and 9.4 Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin-System (RAS) with ACE Inhibitors, ARBs or aliskiren containing drugs.

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, BENAZEPRIL should be discontinued as soon as possible (See 7.1.1 Pregnancy).
- In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system (e.g., patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure), treatment with ACE inhibitor has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death (See 7 Warnings and Precautions, Cardiovascular, 7 Warnings and Precautions, Renal).

4. Dosage and Administration

4.1. Dosing Considerations

Dosage of BENAZEPRIL must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with BENAZEPRIL may need to be adjusted.

In using BENAZEPRIL, consideration should be given to the risk of angioedema (See 7 Warnings and Precautions, Immune, Angioedema).

4.2. Recommended Dose and Dosage Adjustment

Monotherapy

The recommended initial dose of BENAZEPRIL is 10 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks.

The usual maintenance dose is 20 mg daily. The maximum daily dose of BENAZEPRIL is 40 mg.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered.

If blood pressure is not controlled with BENAZEPRIL alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of BENAZEPRIL.

Concomitant Diuretic Therapy

Orthostatic hypotension occasionally may occur following the initial dose of BENAZEPRIL and is more likely in patients who are currently being treated with a diuretic. A cautious dosage schedule or dose reduction should be considered when BENAZEPRIL is initiated in patient on pre-existing diuretic treatment particularly, but not exclusively, in severely sodium-depleted and/or volume depleted patients. This may include temporary dose reduction or suspension of diuretic treatment (e.g., 2 to 3 days) prior to BENAZEPRIL initiation or a reduction of the initial dose of BENAZEPRIL in order to avoid excessive hypotension. If the diuretic cannot be discontinued, an initial dose of 5 mg BENAZEPRIL should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of BENAZEPRIL should subsequently be titrated (as described above) to the optimal response. Volume and/or salt depletion should be corrected before starting therapy with BENAZEPRIL.

Dosage Adjustment in Renal Impairment

The usual dose of BENAZEPRIL is recommended for patients with a creatinine clearance > 30 mL/min [0.5 mL/s]. For patients with severe renal impairment (creatinine clearance of < 30 mL/min [0.5 mL/s]), the initial daily dose is 5 mg. Titration must be individualized. The dosage may be titrated upwards to 10 mg/day. For further reductions in blood pressure, the addition of a diuretic or another antihypertensive should be considered or alternatively, the dose of BENAZEPRIL can be increased. It is not known if benazepril hydrochloride can be removed from the body by hemodialysis.

Pediatrics (<18 years of age)

Health Canada has not authorized an indication for pediatric use.

4.4. Administration

No special considerations regarding administration.

4.5. Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5. Overdose

Although there is very limited experience of overdosage with BENAZEPRIL, the main sign to be expected is severe hypotension, which can be associated with electrolytes disturbances and renal failure.

If ingestion is recent, activated charcoal should be considered. Gastric decontamination (e.g., vomiting, gastric lavage) may be considered in individual cases, in the early period after ingestion.

Patients should be closely monitored for blood pressure and clinical symptoms. Supportive management should be employed to ensure adequate hydration and maintain systemic blood pressure.

In the case of severe hypotension, physiological saline solution should be administered intravenously; depending on the clinical situation the use of vasopressors (e.g., catecholamines i.v.) may be considered.

Although the active metabolite, benazeprilat, is only slightly dialysable, renal dialysis may be useful in overdosed patients with severely impaired renal function.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 5 mg, 10 mg, and 20 mg of benazepril hydrochloride	Colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, red iron oxide (20 mg only), titanium dioxide, yellow iron oxide (5 mg and 10 mg only), and zinc stearate.

BENAZEPRIL 5 mg Tablets: Each light yellow, capsule shaped tablet, engraved "BE" European bisect "5" on one side, plain on the other side, contains 5 mg of benazepril hydrochloride. Available in bottles of 100.

BENAZEPRIL 10 mg Tablets: Each yellow, capsule shaped tablet, engraved "BE" European bisect "10" on one side, plain on the other side, contains 10 mg of benazepril hydrochloride. Available in bottles of 100.

BENAZEPRIL 20 mg Tablets: Each light pink, round shaped, unscored film-coated tablet, plain on one side and engraved "BE" over "20" on the other side contains 20 mg of benazepril hydrochloride. Available in bottles of 100.

7. Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box.

General

Dual Blockade of the Renin-Angiotensin System (RAS): There is evidence that co-administration of angiotensin-converting-enzyme inhibitors (ACEIs), including benazepril hydrochloride, or of angiotensin receptor antagonists (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 benazepril hydrochloride in combination with aliskiren-containing drugs is contraindicated in these patients (See 2 Contraindications). Co-administration of ACE Inhibitors, including benazepril hydrochloride, with other agents blocking the RAS such as ARBs or aliskiren-containing drugs is not recommended in any patient, as adverse outcomes cannot be excluded (See 9.4 Drug-Drug Interactions, Dual blockade of the Renin-Angiotensin-System with ACE Inhibitors, ARBs or aliskiren-containing drugs).

Cardiovascular

Hypotension: Orthostatic hypotension can occur after administration of benazepril hydrochloride tablets usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. (See 8.3 Less Common Clinical Trial Adverse Reactions, Cardiac disorders and Vascular disorders). Because of the potential fall in blood pressure in these patients, therapy with benazepril hydrochloride tablets should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of benazepril hydrochloride tablets is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death (See 3 Serious Warnings and Precautions Box).

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, and usually can be continued without difficulty once the blood pressure has increased after volume expansion. However, decreasing BENAZEPRIL dose and/or reduced concomitant diuretic therapy should be considered.

Valvular Stenosis: Theoretically, 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.

Driving and Operating Machinery

Some adverse effects (e.g., some symptoms of a reduction in blood pressure such as lightheadedness, 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). Caution is recommended with BENAZEPRIL especially at the start of treatment.

Ear/Nose/Throat

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

Endocrine and Metabolism

Hyperkalemia and Potassium-Sparing Diuretics:

Elevated serum potassium (> 5.5 mEq/L) was observed in 1.1% of hypertensive patients in clinical trials treated with benazepril alone and in 0.4% treated with benazepril and hydrochlorothiazide. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in less than 0.1% of hypertensive patients.

Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See 9.4 Drug-Drug Interactions, Agents Increasing Serum Potassium).

Serum potassium should be monitored periodically in patients receiving BENAZEPRIL. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia.

Hepatic/Biliary/Pancreatic

Impaired Liver Function: 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. In most cases the changes were reversed on discontinuation of the drug.

ACE inhibitors 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.

Elevations of liver enzymes and/or serum bilirubin have been reported with benazepril hydrochloride tablets. (See 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data, Hepatic). Should the patient receiving benazepril hydrochloride tablets experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of benazepril hydrochloride tablets should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Benazepril hydrochloride tablets should be used with particular caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before

administration of the drug and close monitoring of response and metabolic effects should apply.

Immune

Angioedema: Angioedema has been reported in patients with ACE inhibitors, including benazepril hydrochloride tablets. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, benazepril hydrochloride tablets should be discontinued immediately, the patient should be 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. Airway obstruction may occur if there is involvement of tongue, glossitis or larynx, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (See 8.3 Less Common Clinical Trial Adverse Reactions, Immune system disorders).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black patients of African origin 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).

Patients receiving co-administration of ACE inhibitors and mTOR (mammalian target of rapamycin) inhibitors (e.g., temsirolimus, sirolimus, everolimus) or a neprilysin inhibitor (e.g., sacubitril) therapy may be at increased risk for angioedema. See 2 Contraindications and 9.4 Drug-Drug Interactions, Drugs Causing Angioedema.

Intestinal Angioedema: Intestinal angioedema has occurred in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angioedema and C-1 esterase levels were normal. In some cases, the angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor.

Anaphylactoid and related reactions: Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including benazepril hydrochloride tablets) may experience a variety of adverse reactions, some of them serious.

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

Anaphylactoid Reactions During Desensitization: BENAZEPRIL must be withdrawn at least 24

hours prior to desensitization therapy. 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.

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 benazepril hydrochloride tablets (See 9.4 Drug-Drug Interactions, Gold).

Monitoring and Laboratory Tests

Neutropenia/Agranulocytosis:

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Current experience with benazepril hydrochloride tablets shows that the incidence is rare and a causal relationship to the administration of benazepril hydrochloride tablets has not been established. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Perioperative Considerations

Surgery/Anesthesia: Patients on ACE inhibitors may augment the hypotensive effects of anesthetics and analgesics. In patients undergoing surgery or during anesthesia with agents that cause hypotension, benazepril hydrochloride will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Renal

Renal Impairment: The use of ACE Inhibitors – including benazepril hydrochloride tablets – or of ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60 mL/min/1.73m^2) (See 2 Contraindications and 9.4 Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACE Inhibitors, or aliskiren-containing drugs).

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function depends on the activity of the renin-angiotensin-aldosterone system, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death (See 3 Serious Warnings and Precautions Box). In susceptible patients, concomitant diuretic use may further increase risk.

Use of BENAZEPRIL (benazepril hydrochloride) should include appropriate assessment of renal function (See 4.2 Recommended Dose and Dosage Adjustment).

7.1. Special Populations

7.1.1. Pregnancy

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, BENAZEPRIL should be discontinued as soon as possible (See 2 Contraindications).

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, and is associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Perform serial ultrasound examinations to assess the intra-amniotic environment.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure to ACE inhibitors 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.

7.1.2. Breastfeeding

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is contraindicated during breast-feeding (See 2 Contraindications).

7.1.3. Pediatrics

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

7.1.4. Geriatrics

Geriatrics (> 65 years of age): Over 400 elderly patients have participated in controlled hypertension trials, and no increased incidence of adverse reactions was observed compared to younger patients. Although clinical experience has not identified differences in response between the elderly (> 65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Benazepril hydrochloride tablets has been evaluated for safety in over 6,000 hypertensive patients. Long-term safety has been assessed in more than 700 patients treated for 1 year or more. The overall frequency of adverse reactions was not related to duration of therapy or total daily dose.

The most severe adverse reactions occurring in clinical trials with benazepril hydrochloride tablets were: angioedema (full clinical syndrome, 1 case; edema of lips or face without the other manifestations of angioedema, 0.5%), hypotension (0.3%), postural hypotension (0.4%) and syncope (0.1%) (See 7 Warnings and Precautions, Immune, Angioedema). Hypotension or postural dizziness was a cause for discontinuation of therapy in < 0.2% of patients treated with benazepril hydrochloride alone. Myocardial infarction and cerebral vascular accident occurred, possibly secondary to excessive hypotension in high risk patients (See 7 Warnings and Precautions, Cardiovascular, Hypotension).

The most frequent clinical adverse reactions in placebo-controlled clinical trials with benazepril hydrochloride monotherapy (N=964) were headache (6.2%), dizziness (3.6%), fatigue (2.4%), somnolence (1.6%), postural dizziness (1.5%), nausea (1.3%) and cough (1.2%). Discontinuation of therapy due to adverse experiences was required in 4% of patients treated with benazepril hydrochloride.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Adverse reactions occurring in 1% or more of the 2004 patients in controlled hypertension trials who were treated with benazepril hydrochloride monotherapy, are listed below:

Table 2 - Reported adverse reactions according to body systems

	Benazepril hydrochloride Patients (N=2004) (%)
Gastrointestinal disorders	
Nausea	2.5%
Abdominal pain	2.4%
Diarrhea	2.0%
Dyspepsia	1.2%

	Benazepril hydrochloride Patients (N=2004) (%)
General disorders and administration site conditions	
Fatigue	3.6%
Chest Pain	1.2%
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	2.6%
Back Pain	1.7%
Nervous system disorders	
Headache	10.2%
Dizziness	4.2%
Somnolence	1.1%
Vertigo	1.1%
Respiratory, thoracic and mediastinal disorders	
Symptoms of upper respiratory tract infection	5.4%
Increased cough	3.4%
Rhinitis	2.4%
Pharyngitis	1.7%
Flu symptoms	1.2%

8.3. Less Common Clinical Trial Adverse Reactions

Clinical adverse reactions occurring in less than 1% of patients treated with benazepril hydrochloride tablets in controlled and uncontrolled clinical trials, and post-marketing experience, are listed below by body system:

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

Blood and lymphatic system disorders: leucopenia, eosinophilia, hemolytic anemia and thrombocytopenia.

Cardiac disorders: angina pectoris, palpitations, myocardial infarction, arrhythmia.

Ear and labyrinth disorders: tinnitus.

Gastrointestinal disorders: constipation, gastritis, vomiting, flatulence, melena, abdominal pain, pancreatitis, taste disorders.

General disorders and administration site conditions: asthenia.

Hepatobiliary disorders: hepatitis (predominantly cholestatic), cholestatic jaundice.

Immune system disorders: angioedema, lip edema, face edema.

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

Nervous system disorders: hypertonia, insomnia, paresthesia, incoordination.

Psychiatric disorders: anxiety, depression, nervousness.

Renal and urinary disorders: impaired renal function, pollakiuria.

Reproductive system and breast disorders: decreased libido, impotence.

Respiratory, thoracic, and mediastinal disorders: dyspnea, asthma, bronchitis.

Skin and subcutaneous tissue disorders: apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, pemphigus, flushing, Stevens-Johnson Syndrome.

Vascular disorders: excessive hypotension, cerebrovascular accident.

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

Hyperkalemia: See 7 Warnings and Precautions, Endocrine and Metabolism.

Creatinine, Blood Urea Nitrogen: Increases in serum creatinine (> 150% of baseline) were observed in 2% of patients treated with benazepril hydrochloride tablets alone. Less than 0.1% of these patients developed simultaneous increases in blood urea nitrogen and serum creatinine. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on benazepril hydrochloride tablets alone. These increases often reversed on continued therapy.

Neutropenia: Neutrophil counts of less than 1500/mm^3 occurred in 2% of patients treated with benazepril hydrochloride tablets alone. No patient was discontinued from a study because of a low neutrophil or white blood cell (WBC) count. No patient developed a persistent neutrophil count < 1000/mm^3 and no patient developed a serious infection in association with a reduced neutrophil or WBC count. No patient treated with benazepril hydrochloride tablets developed agranulocytosis (See 7 Warnings and Precautions, Monitoring and Laboratory Tests).

Hemoglobin: Decreases in hemoglobin (a low value and a decrease of 5 g/dL) occurred in only 1 out of 2014 patients receiving benazepril hydrochloride tablets alone and in 1 out of 1357 patients receiving benazepril hydrochloride tablets plus a diuretic.

Hepatic: Elevations of liver enzymes and/or serum bilirubin have occurred (See 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

Other: Elevations of uric acid and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, and proteinuria.

8.5. Post-Market Adverse Reactions

The following adverse events of unknown frequency have been reported during post-marketing use of BENAZEPRIL:

Blood and lymphatic system disorders: agranulocytosis, neutropenia.

Eye disorders: impaired vision (e.g., blurred vision, metamorphopsia, scotoma, and temporary vision loss).

Gastrointestinal disorders: small bowel angioedema.

Immune system disorders: anaphylactoid reactions.

Metabolism and nutrition disorders: hyperkalemia (See 7 Warnings and Precautions).

Renal and urinary disorders: urinary tract infection.

Respiratory, thoracic and mediastinal disorders: sinusitis.

Skin and subcutaneous tissue disorders: alopecia, sweating.

9. Drug Interactions

9.1. Serious Drug Interactions

- Contraindicated in the concomitant use with a neprilysin inhibitor (e.g., sacubitril, see 9.4 Drug-Drug Interactions, Drugs causing angioedema)
- Contraindicated in the concomitant use with aliskiren-containing drugs in patients with diabetes or moderate to severe renal impairment (See 9.4 Drug-Drug Interactions, Dual blockade of the Renin-Angiotensin-System with ACE Inhibitors, ARBs or aliskiren-containing drugs)

9.2. Drug Interactions Overview

Benazepril hydrochloride is hydrolyzed to the active metabolite benazeprilat, which inhibits the ACE and blocks the conversion of angiotensin I to angiotensin II. Pharmacokinetics and pharmacodynamics of active metabolite can be influenced by the drugs which are co-administered.

9.3. Drug-Behaviour Interactions

The interaction of BENAZEPRIL with individual behavioural risks (e.g., cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

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 3 - Established or Potential Drug-Drug Interactions for benazepril

Non-proprietary names of the drug products	Source of Evidence	Effect	Clinical comment
Agents Causing Renin Release (e.g., diuretics)	CT	The antihypertensive effect of benazepril hydrochloride tablets is increased by antihypertensive agents that cause renin release (e.g., diuretics).	Close monitoring of blood pressure and dose adjustment may be required if coadministration of benazepril hydrochloride tablets with agents causing renin release cannot be avoided.
Agents Increasing Serum Potassium	CT, C	Since benazepril hydrochloride tablets decreases aldosterone production, increases of serum potassium may occur. Concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride, etc.) or potassium supplements and other drugs (e.g., cyclosporine, heparin) is not recommended in patients receiving ACE inhibitors (including benazepril hydrochloride tablets) and should be given only for documented hypokalemia and with caution, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.	Frequent monitoring of serum potassium level.
Agents Affecting	CT	Agents affecting	Close monitoring of blood

Non-proprietary names of the drug products	Source of Evidence	Effect	Clinical comment
Sympathetic Activity		sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. β-adrenergic blocking agents enhance the antihypertensive effect of benazepril hydrochloride tablets.	pressure and dose adjustment may be required if coadministration of benazepril hydrochloride tablets with agents affecting sympathetic activity cannot be avoided.
Amlodipine/Nifedipine	CT	Benazepril hydrochloride tablets has been used concomitantly with calcium channel blockers amlodipine and nifedipine, without evidence of clinically important adverse interactions.	
Digoxin	CT	In a single dose interaction study of benazepril hydrochloride tablets with multiple doses of digoxin, no important changes in pharmacokinetic parameters were observed.	
Diuretics	C	Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may experience an excessive reduction of blood pressure after initiation of therapy.	The possibility of hypotensive effects after the first dose of benazepril hydrochloride tablets can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of benazepril hydrochloride tablets. If it is not possible to discontinue the diuretic, the starting dose of benazepril hydrochloride tablets should be reduced and the patient should be closely observed for several

Non-proprietary names of the drug products	Source of Evidence	Effect	Clinical comment
			hours following initial dose and until blood pressure has stabilized (See 7 Warnings and Precautions, Cardiovascular, Hypotension and 4.2 Recommended Dose and Dosage Adjustment, Concomitant Diuretic Therapy).
Drugs causing angioedema	CT, C	The risk of angioedema may be increased in patients receiving co-administration of ACE inhibitors and drugs such as dipeptidyl peptidase-IV inhibitors or mTOR inhibitors (e.g., temsirolimus, sirolimus, and everolimus) or neprilysin inhibitors (e.g., sacubitril) (See 2 Contraindications and 7 Warnings and Precautions, Immune, Angioedema).	Close monitoring may be required if concomitant administration cannot be avoided. BENAZEPRIL must not be administered within 36 hours of switching to or from a neprilysin inhibitor (e.g., sacubitril/valsartan). Concomitant treatment with a neprilysin inhibitor (e.g., sacubitril/valsartan) is contraindicated.
Dual blockade of the Renin-Angiotensin-System (RAS) with ACE Inhibitors, ARBs or aliskiren-containing drugs	CT	There is evidence that co-administration of angiotensin-converting-enzyme inhibitors (ACEIs), including benazepril hydrochloride tablets, or of angiotensin receptor antagonists (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	The use of benazepril hydrochloride tablets in combination with aliskiren-containing drugs is contraindicated in these patients (See 2 Contraindications). Co-administration of ACE Inhibitors, including benazepril hydrochloride tablets, with other agents blocking the RAS such as ARBs or aliskiren-containing drugs is not recommended in any patient, as adverse

Non-proprietary names of the drug products	Source of Evidence	Effect	Clinical comment
		severe renal impairment (GFR<60 mL/min/1.73m^2).	outcomes cannot be excluded. Closely monitor blood pressure, renal function and electrolytes in patients on BENAZEPRIL and other agents that affect the RAS.
Erythropoietin	T	Patient responsiveness to erythropoietin may decrease when use concomitantly with ACE inhibitors (including benazepril hydrochloride tablets).	
Gold	T	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.	Close monitoring of blood pressure may be required when coadministration with benazepril hydrochloride tablets cannot be avoided.
Hydrochlorothiazide, Chlorthalidone and Furosemide	CT	The bioavailability of benazepril hydrochloride tablets was not altered when single doses were administered concomitantly with the diuretics hydrochlorothiazide, chlorthalidone or furosemide.	
Insulin/Oral anti-diabetics	C	ACE inhibitors (including benazepril hydrochloride tablets) may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycemic reactions in patients treated	Particularly close blood glucose monitoring is recommended. In case of persistent and/or severe hypoglycemia, dose adjustment or discontinuation of

Non-proprietary names of the drug products	Source of Evidence	Effect	Clinical comment
		concomitantly with anti-diabetics.	benazepril hydrochloride tablets should be considered.
Lithium	C	Increased lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors (including benazepril hydrochloride tablets) during therapy with lithium.	These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT, C	It has been shown that the hypotensive effect of ACE inhibitors may be reduced when administered concomitantly with indomethacin and other non-steroidal anti-inflammatory drugs. In a controlled clinical trial, indomethacin did not interfere with the antihypertensive effect of benazepril hydrochloride tablets and no important changes in pharmacokinetic parameters occurred when single doses of benazepril hydrochloride tablets were administered concomitantly with acetylsalicylic acid. The combination of non-steroidal anti-inflammatory drugs and ACE inhibitors, (including benazepril hydrochloride tablets) can increase the risk of renal impairment and hyperkalemia.	Monitoring of renal function and potassium level is recommended.
Oral Anticoagulants	CT	Multiple dose interaction studies failed to identify any	

Non-proprietary names of the drug products	Source of Evidence	Effect	Clinical comment
		clinically important effects on the serum concentrations, the degree of protein binding or the anticoagulant effect (measured by prothrombin time) of warfarin and nicoumalone. The bioavailability of benazeprilat was not assessed during the coadministration of benazepril hydrochloride with warfarin or nicoumalone.	
Other agents with antihypertensive properties	CT	Benazepril hydrochloride tablets may increase the hypotensive effect of other antihypertensive agents.	Dosages must be adjusted accordingly.
Probenecid	CT	Probenecid pretreatment may enhance the pharmacodynamic response of ACE inhibitors.	Dose adjustment may be necessary.
Propranolol, naproxen, atenolol, nifedipine or cimetidine	CT	In separate single or multiple dose pharmacokinetic interaction studies, the bioavailability of benazepril hydrochloride tablets was not altered by coadministration with propranolol, naproxen, atenolol, nifedipine or cimetidine.	

Legend: C = Case 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

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Benazepril hydrochloride tablets is an angiotensin converting enzyme (ACE) inhibitor.

Benazepril hydrochloride, after hydrolytic bioactivation to benazeprilat, inhibits angiotensin converting enzyme (ACE), a peptidyl dipeptidase catalyzing the conversion of angiotensin I to the vasoconstrictor angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex, leading to sodium resorption and potassium secretion by the distal renal tubules.

Inhibition of ACE results in a decrease in plasma angiotensin II, leading to decreased vasoconstriction and a small decrease in aldosterone secretion and plasma aldosterone concentrations. Although the decrease in aldosterone is small, it can result in small increases in serum potassium. See 7 Warnings and Precautions, Endocrine and Metabolism. Angiotensin II also inhibits renin secretion, thus, decreased level of angiotensin II leads to increased plasma renin activity.

ACE is identical to kininase II. Thus, benazepril hydrochloride may interfere with degradation of the potent peptide vasodilator, bradykinin. Whether increased levels of bradykinin play a role in the therapeutic effects of benazepril hydrochloride is unknown.

While the mechanism through which benazepril hydrochloride lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril hydrochloride tablets has an antihypertensive effect even in patients with low renin hypertension.

10.2. Pharmacodynamics

Administration of benazepril hydrochloride tablets to patients with mild to moderate essential hypertension results in a reduction of both supine and standing blood pressure, usually with little or no orthostatic change. Orthostatic hypotension is infrequent, although it may occur in patients who are salt- and/or volume-depleted (See 7 Warnings and Precautions, Cardiovascular, Hypotension).

After administration of a single oral dose, the onset of antihypertensive activity occurs at approximately one hour, with maximum reduction of blood pressure achieved by 2 to 4 hours in most patients. At recommended doses given once daily, antihypertensive effects have persisted for at least 24 hours. In dose-response studies using once daily dosing in mild to moderate essential hypertensive patients, the minimally effective daily dose of benazepril

hydrochloride tablets was 10 mg. In studies comparing the same daily dose of benazepril hydrochloride tablets given as a single morning dose or as a twice daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

During chronic therapy, the maximum reduction in blood pressure with any dose is generally achieved after 1 to 2 weeks. Abrupt withdrawal of benazepril hydrochloride tablets has not been associated with a rapid increase in blood pressure.

When benazepril hydrochloride is given together with thiazide-type diuretics, its blood pressure lowering effect is approximately additive.

In animal studies, benazepril hydrochloride tablets had no inhibitory effect on the vasopressor response to angiotensin II, and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine and norepinephrine.

10.3. Pharmacokinetics

Absorption

Following oral administration of benazepril hydrochloride tablets, peak plasma concentrations of benazepril are reached within 0.5 to 1.0 hours. The extent of absorption is at least 37% as determined by urinary recovery of unchanged drug and its metabolites. Following absorption, benazepril hydrochloride is rapidly hydrolyzed to its active metabolite benazeprilat. Peak plasma concentrations of benazeprilat are reached 1 to 2 hours after drug intake in the fasting state and 2 to 4 hours after drug intake in the non-fasting state. While the rate of absorption may be slowed by the presence of food in the gastrointestinal tract, the systemic availability of benazeprilat is not affected.

Distribution

Only trace amounts of an administered dose of benazepril hydrochloride can be recovered in the urine as unchanged benazepril, while about 20% of the dose is excreted as benazeprilat, 4% as benazepril glucuronide, and 8% as benazeprilat glucuronide. The kinetics of benazepril hydrochloride tablets are approximately dose-proportional within the dosage range (10 to 40 mg).

Benazepril hydrochloride passes the blood-brain barrier only to an extremely low extent, as evidenced by studies in rats with ^{14}C-labelled benazepril, in which the lowest concentration of radioactivity was found in the brain (0.14 mg/g compared to blood concentrations of 3 to 4.5 mg/g). Multiple doses of benazepril hydrochloride resulted in relatively high concentrations for a short period of time in liver and excretory organs (renal and biliary excretion). No particular tissue affinity was observed except for a slight increase in concentration in the lung, due to slower elimination in that organ.

Metabolism

Benazepril hydrochloride is almost completely metabolized to benazeprilat, and to the glucuronide conjugates of benazepril and benazeprilat.

Elimination

Benazeprilat is eliminated predominantly by renal excretion and has an effective accumulation half-life of 10 to 11 hours. The serum protein binding of benazepril is about 97%, and that of benazeprilat about 95%.

Special Populations and Conditions

- **Pediatrics:** No data available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.
- **Geriatrics:** The pharmacokinetics of benazepril hydrochloride and benazeprilat do not appear to be influenced by age.

  Efficacy and safety appear to be the same for elderly (> 65 years of age) and younger adult patients given the same daily dosages.
- **Sex**: This information is not available for this drug product.
- **Pregnancy and Breast-feeding:** When pregnancy is detected, benazepril hydrochloride should be discontinued as soon as possible.

  Use of ACE inhibitors is contraindicated during breast-feeding. Some placental passage occurred when the drug was administered to pregnant rats.
- **Genetic Polymorphism**: This information is not available for this drug product.
- **Ethnic Origin:** ACE inhibitors, including benazepril hydrochloride tablets, as monotherapy, have an effect on blood pressure that is less in Black patients than in non-Blacks.
- **Hepatic Insufficiency:** In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered.
- **Renal Insufficiency:** The disposition of benazepril hydrochloride and benazeprilat in patients with mild to moderate renal insufficiency (creatinine clearance > 30 mL/min [0.5 mL/s]) is similar to that in patients with normal renal function. In patients with creatinine clearance < 30 mL/min [0.5 mL/s], peak benazeprilat levels and the initial (alpha phase) half-life increase, and time to steady state may be delayed (See 4.2 Recommended Dose and Dosage Adjustment, Dosage Adjustment in Renal Impairment).
- **Obesity:** This information is not available for this drug product.

11. Storage, Stability, and Disposal

Store at room temperature (15°C - 30°C).

Part 2: Scientific Information

13. Pharmaceutical Information

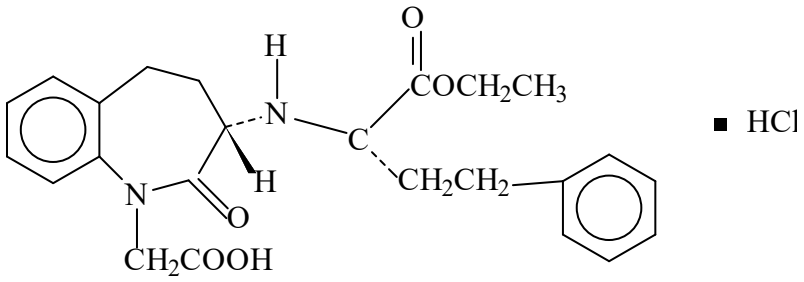
Drug Substance

Proper name: Benazepril Hydrochloride

Chemical name: 3-[(1 -(Ethoxycarbonyl)-3-phenyl-(1S)-propyl) amino]-2,3,4,5-tetrahydro-2-oxo- 1 H-1 -(3S)-benzazepine- 1-acetic acid monohydrochloride

Molecular formula and molecular mass: $C_{24}H_{28}N_2O_5.HCl$ and 460.96 g/mol

Structural formula:



Physicochemical properties:

Description:	Practically odourless, white to off-white powder.
pH:	2.4
pKa:	4.55
Melting Point:	188 to 190°C
Water/Octanol Partition Coefficient:	3.5 (Benazepril)

Quantitative aqueous pH solubility profile:

Solvent	pH	Solubility (mg/mL)
0.1N HCl	1.2	>100
Water	1.9	>100
0.05 M Phosphate Buffer	2.3	>20
0.05 M Phosphate Buffer	2.4	9.2

Solvent	pH	Solubility (mg/mL)
0.05 M Phosphate Buffer	2.5	6.6
0.05 M Phosphate Buffer	3.2	2.1
0.05 M Phosphate Buffer	5.3	3.8
0.05 M Phosphate Buffer	5.9	6.6
0.05 M Phosphate Buffer	6.1	8.2
0.05 M Phosphate Buffer	6.3	8.7
0.05 M Phosphate Buffer	7.1	14.0

14. Clinical Trials

14.2 Comparative Bioavailability Studies

Comparative bioavailability studies were performed on the 5 mg strength and the 20 mg strength.

Comparative Bioavailability – 5 mg Strength

For the 5 mg strength, a double-blind, randomized, two-way, single-dose crossover comparative bioavailability study was performed on 19 healthy adult male volunteers under fasting conditions. The rate and extent of absorption of benazepril was measured and compared following a 10 mg single oral dose (2 x 5 mg) of BENAZEPRIL (benazepril hydrochloride) (AA Pharma Inc.) or LOTENSIN® (Novartis Pharmaceuticals Canada Inc.) tablets. The results from measured data are summarized as follows:

Table 4 - Summary Table of the Comparative Bioavailability Data – 5 mg Strength

Benazepril (2 x 5 mg) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%)				
Parameter	**BENAZEPRIL§**	**LOTENSIN® †**	**% Ratio of Geometric Means****	**90% Confidence interval****
AUC_T (ng·hr/mL)	193 201 (27)	204 211 (27)	94.7	88.1 – 102
AUC_I (ng·hr/mL)	195 202 (27)	206 213 (27)	94.7	88.1 – 102
C_{max} (ng/mL)	250 259 (26)	260 269 (25)	96.3	84.2 - 110
T_{max} (hr)*	0.40 (32)	0.45 (28)		

Benazepril (2 x 5 mg) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%)				
Parameter	**BENAZEPRIL§**	**LOTENSIN® †**	**% Ratio of Geometric Means****	**90% Confidence interval****
$t_{1/2}$ (hr)*	1.10 (17)	1.10 (15)		

* Expressed as the arithmetic mean (CV%) only.
§ Benazepril Hydrochloride 5 mg Tablets (AA Pharma Inc.)
** Based on least squares estimate.
† LOTENSIN® is manufactured by Novartis Pharmaceuticals Canada Inc., and was purchased in Canada

Comparative Bioavailability – 20 mg Strength

For the 20 mg strength, a double-blind, randomized, two-way, single-dose crossover comparative bioavailability study was performed on 18 healthy adult male volunteers under fasting conditions. The rate and extent of absorption of benazepril was measured and compared following a 20 mg single oral dose (1 x 20 mg) of BENAZEPRIL (benazepril hydrochloride) (AA Pharma Inc.) or LOTENSIN® (Novartis Pharmaceuticals Canada Inc.) tablets. The results from measured data are summarized as follows:

Table 5 - Summary Table of the Comparative Bioavailability Data – 20 mg Strength

Benazepril (1 x 20 mg) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%) Based on Benazepril				
Parameter	**BENAZEPRIL§**	**LOTENSIN® †**	**% Ratio of Geometric Means****	**90% Confidence interval****
AUC_T (ng·hr/mL)	216 231 (35)	209 219 (30)	103.3	96.8 – 110.2
AUC_I (ng·hr/mL)	219 233 (35)	211 221 (30)	103.3	96.9 – 110.1
C_{max} (ng/mL)	311 336 (39)	293 307 (30)	104.2	92.3 – 117.5
T_{max} (hr)*	0.43 (28)	0.47 (27)		

Benazepril (1 x 20 mg) From Measured Data Uncorrected for potency Geometric Mean Arithmetic Mean (CV%) Based on Benazepril				
Parameter	**BENAZEPRIL[§]**	**LOTENSIN®[†]**	**% Ratio of Geometric Means[**]**	**90% Confidence interval[**]**
$t_{1/2}$ (hr)[*]	1.08 (18)	1.06 (19)		

[*] Expressed as the arithmetic mean (CV%) only.
[§] Benazepril Hydrochloride 20 mg Tablets (AA Pharma Inc.)
[**] Based on least squares estimate.
[†] LOTENSIN® is manufactured by Novartis Pharmaceuticals Canada Inc., and was purchased in Canada

16. Non-Clinical Toxicology

General Toxicology

Signs of toxicity in rodents include ptosis, reduced activity, exophthalmus, bradypnea, clonic spasms and dyspnea.

Intravenous doses of 2.5 mg/kg induced no adverse effects in the female beagle. Emesis and anorexia were noted in beagles given oral doses ≥ 250 mg/kg and ≥ 500 mg/kg respectively. One dog was found dead on the fifth day post-dose after daily signs of emesis, anorexia, nasal discharge and reduced activity.

Repeated Dose Toxicity Studies

Rats (52 Weeks):

A 52-week study in rats involved the administration of the benazepril hydrochloride through their diet at doses of 0, 10, 50, and 250 mg/kg in both sexes. The study found no compound-related mortalities, but there were several physiological and biochemical effects. Erythroid parameters decreased at doses ≥50 mg/kg. There was an increase in the percentage of reticulocytes in females at the highest dose (250 mg/kg) and increases in serum potassium (K+) were observed in males at doses ≥50 mg/kg, and chloride (Cl-) in both sexes at doses ≥10 mg/kg. BUN levels also increased at doses ≥50 mg/kg. There were consistent reductions in food consumption and body weight gain across all dose groups. Histopathological findings included hypertrophy of JG cells and arterioles, and reduced kidney and liver weights. At the highest doses, there was also a reduction in absolute and/or relative heart weight, with prostate weight increasing in males at doses ≥50 mg/kg and thymus weight at doses ≥250 mg/kg. While some changes were observed, there were no severe or irreversible effects. The No Observed Adverse Effect Level (NOAEL) was selected as 10 mg/kg in rats, which is approximately 2 times the maximum recommended human dose.

Dogs (12 Months):

A 12-month study in dogs involved oral administration of benazepril hydrochloride at doses of 0, 15, 50, and 150 mg/kg, administered via capsules. No mortality or clinical signs related to the compound were observed during the study. However, food consumption and body weight gain were reduced in males at doses ≥50 mg/kg. Biochemically, there were increases in BUN and changes in erythroid parameters at certain time points at doses ≥50 mg/kg. Heart rate (HR) increased at the highest dose (≥150 mg/kg), and there was some evidence of splenic hemosiderosis, as well as mild renal cortical tubular basophilia and interstitial inflammation at the highest dose (150 mg/kg). JG cell and arteriolar hypertrophy were seen across all doses. However, these effects were reversible after a 1-month recovery period. The NOAEL was selected as 15 mg/kg in dogs, which is approximately 10.4 times the maximum recommended human dose.

Carcinogenicity

No evidence of a tumorigenic effect was seen when benazepril hydrochloride tablets was administered for 104 weeks to rats at a dose of up to 150 mg/kg/day (30.2 times the maximum recommended human dose). No evidence of carcinogenicity was seen when benazepril hydrochloride tablets was administered for up to 104 weeks to mice at the same dose.

Genotoxicity

Benazepril was not mutagenic when tested in the Ames microbial mutagen test with or without metabolic activation. The following genotoxicity studies with benazepril hydrochloride tablets were negative: an *in vitro* test for forward mutations in cultured mammalian cells, a nucleus anomaly test, and a sister chromatid exchange study in Chinese hamsters.

Reproductive and Developmental Toxicology

No adverse effects on reproductive performance were observed in male and female rats treated with 50 to 500 mg/kg/day of benazepril hydrochloride during gestational days 6 through 15 or from 14 days premating to 21 days postpartum. The NOAEL was selected as 500 mg/kg/day, which is approximately 100.8 times the maximum recommended human dose.

No direct embryotoxic, fetotoxic or teratogenic effects were seen in rats, mice or rabbits treated during gestational days 6 to 15 (mice and rats) or 7 to 19 (rabbits) with oral doses up to 500 mg/kg/day in rats (100.8 times the maximum recommended human dose), 150 mg/kg/day in mice (15.23 times the maximum recommended human dose) and 5 mg/kg/day in rabbits (3 times the maximum recommended human dose), respectively. Fetal effects consisted of developmental delays secondary to maternal toxicity (decreased food consumption and body weight). Postnatal growth of rat pups was reduced at maternal doses ≥ 250 mg/kg/day. Maternal toxicity with mortality occurred in rabbits at doses of 0.1 mg/kg/day or more.

Dose related maternal toxicity was observed in studies of pregnant rats, mice and rabbits at doses of 250 mg/kg, 150 mg/kg and 1 mg/kg (0.4 times the maximum recommended dose in humans) respectively. No embryotoxic or teratogenic effects of benazepril hydrochloride

tablets were seen at doses up to 250 mg/kg in rats (300 times the maximum recommended dose in humans), 150 mg/kg in mice (90 times the maximum recommended dose in humans) and 5 mg/kg in rabbits (more than 3 times the maximum recommended dose in humans).

Juvenile toxicity

No information available.

Special toxicity

No information available.

17. Supporting Product Monographs

1 LOTENSIN® (benazepril hydrochloride tablets 5 mg and 20 mg), submission control number 216946, Product Monograph, Novartis Pharmaceuticals Canada Inc. (SEP 20, 2018)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBENAZEPRIL

Benazepril Hydrochloride Tablets

This Patient Medication Information is written for the person who will be taking **BENAZEPRIL**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **BENAZEPRIL**, talk to a healthcare professional.

Serious warnings and precautions box

- If you are pregnant, BENAZEPRIL poses a risk to your unborn baby. This can affect your baby's growth or even cause death. If you think you are pregnant while taking BENAZEPRIL, stop your treatment right away and tell your healthcare professional.
- BENAZEPRIL can also cause severe hypotension (low blood pressure). This is more likely to happen if you have certain heart or kidney problems. Tell your healthcare professional if you have any heart or kidney problems before you start your treatment.

What BENAZEPRIL is used for:

- the treatment of high blood pressure in adults. It can be used alone or together with other medicines for high blood pressure known as thiazide diuretics.

How BENAZEPRIL works:

BENAZEPRIL belongs to a group of medicines known as "angiotensin converting enzyme (ACE) inhibitors". These work to help widen blood vessels that make it easier for the heart to pump blood.

The ingredients in BENAZEPRIL are:

Medicinal ingredients: Benazepril hydrochloride.

Non-medicinal ingredients: Colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, red iron oxide (20 mg only), titanium dioxide, yellow iron oxide (5 mg and 10 mg only), and zinc stearate.

BENAZEPRIL comes in the following dosage forms:

Tablets: 5 mg, 10 mg, and 20 mg of benazepril hydrochloride.

Do not use BENAZEPRIL if:

- you are allergic to benazepril hydrochloride or to any other ingredients in BENAZEPRIL.
- you previously had an allergic reaction that caused angioedema (i.e., swelling of the hands, feet, or ankles, face, lips, tongue, or throat).
- you are pregnant or planning to become pregnant. Taking BENAZEPRIL during pregnancy can cause injury and even death to your baby.
- you are breastfeeding or planning to breastfeed. BENAZEPRIL passes into breast milk.
- you have diabetes or kidney problems, and you are taking medicines containing aliskiren (used to treat high blood pressure).
- you are taking other medicines used to treat high blood pressure called "neprilysin inhibitors" (e.g., sacubitril, or sacubitril and valsartan). Do **not** take BENAZEPRIL and neprilysin inhibitors within 36 hours of each other.

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

- have had an allergic reaction causing swelling of your face, lips, tongue or throat (angioedema).
- have recently received or are planning to get allergy (desensitization) shots for bee or wasp stings. Your healthcare professional will tell you to temporarily stop taking BENAZEPRIL at least 24 hours before you get your allergy shots. This will help prevent you from having a serious allergic reaction. You should also tell the healthcare professional who is giving you the shot that you are taking BENAZEPRIL.
- have heart or blood vessel problems.
- have liver problems.
- have kidney problems.
- have diabetes.
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- are on dialysis or planning to start dialysis.
- have low sodium levels or are on a low-salt (low sodium) diet.
- have an autoimmune disease where the body attacks the collagen in your tissues known as a "collagen vascular diseases". This happens when the body reacts against its own tissues, often causing joint pain and inflammation (e.g., systemic lupus erythematosus or scleroderma).
- are having a surgery or planning to have a surgery, especially if you will be given an anesthetic.
- are on a treatment to lower cholesterol in the blood, such as low-density lipoproteins (LDL) apheresis.

Other warnings you should know about:

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

Driving and using machines: BENAZEPRIL can cause lightheadedness, dizziness, and fainting, especially at the start of your treatment. Before you perform tasks which may require special attention, wait until you know how you respond to BENAZEPRIL.

Check-ups and testing: Your healthcare professional will assess your health before, during, and after your treatment with BENAZEPRIL. This will depend on your health condition and may include certain tests to assess the following:

- your blood pressure;
- your heart, kidneys, and liver; and/or
- the make-up of your blood (e.g., levels of glucose, potassium, and white blood cells in your blood).

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

Serious drug interactions:

Serious drug interactions with BENAZEPRIL include:

- neprilysin inhibitors (e.g., sacubitril alone, or sacubitril with valsartan), used to treat chronic heart failure.
- medicines that contain aliskiren, used to treat high blood pressure, especially if you also have diabetes or certain kidney problems.

The following may also interact with BENAZEPRIL:

- anticoagulants, used to thin the blood or prevent blood clots (e.g., heparin, warfarin, and nicoumalone).
- anti-diabetics, used to treat diabetes (e.g., insulin).
- cyclosporine, used to help prevent organ rejection.
- diuretics, also known as the “water pill”, used to increase the amount of water released in the urine (e.g., hydrochlorothiazide, chlorthalidone, and furosemide).
- erythropoietin, used to regulate the production of red blood cells.
- injectable gold (sodium aurothiomalate), used to treat a disease that affects your joints known as rheumatoid arthritis.
- lithium, used to treat some types of depression.
- medicines that affect the sympathetic nervous system (e.g., ganglionic blocking agents and adrenergic neuron blocking agents).
- medicines that can affect white blood cells or the immune system (e.g., mTOR inhibitors such as temsirolimus, sirolimus, and everolimus).
- medicines that can increase the level of potassium in the blood (e.g., salt substitutes containing potassium, potassium supplements, and potassium-sparing diuretics such as spironolactone, triamterene, and amiloride).

- non-steroidal anti-inflammatory drugs (NSAIDs), used to treat pain, fever and inflammation (e.g., indomethacin, naproxen, and acetylsalicylic acid).
- other medicines used to treat high blood pressure (e.g., angiotensin receptor blockers (ARBs), beta blockers such as propranolol and atenolol, and calcium channel blockers such as amlodipine and nifedipine).
- probenecid, used to treat gout.

If you are unsure, ask your healthcare professional.

How to take BENAZEPRIL:

- Take BENAZEPRIL exactly as directed by your healthcare professional. If you are unsure, check with your healthcare professional.
- It is recommended to take your dose at about the same time every day.
- Swallow your tablet with a glass of water.
- Never change the dose unless told to do so.

Usual dose:

Your healthcare professional will determine the right dose of BENAZEPRIL for you. This will depend on your health, if you take other medicines, and how you respond to BENAZEPRIL. Do **not** change your dose unless told by your healthcare professional.

The usual initial dose is 10 mg per day, which may be increased by your healthcare professional up to a maximum of 40 mg per day.

Overdose:

If you think you, or a person you are caring for, have taken too much BENAZEPRIL, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss or forgot to take a dose of this medicine, take the missed dose as soon as possible. If it is almost time for your next dose, skip the missed dose and then take the next one at the usual time. Do **not t**ake a double dose to make up for the missed dose.

Possible side effects from using BENAZEPRIL:

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

Side effects of BENAZEPRIL may include:

- drowsiness;
- cough (dry, non-productive, mainly at night, continuing);
- sore throat and throat irritation;
- headache;
- flushing;
- numbness or tingling in the hands, feet or lips;
- ringing in the ears;
- loss or change of taste;
- loss or change of taste;
- erectile dysfunction (difficulty getting or keeping an erection);
- decreased sex drive;
- musculoskeletal pain (e.g., back pain, stiff muscles joint swelling or pain, muscle pain, tenderness, or weakness);
- vertigo;
- common cold;
- runny nose;
- passing more gas than usual;
- feeling nervous;
- urinary tract infection (pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, or cloudy urine);
- face pain;
- stuffy or runny nose;
- sweating;
- hair loss

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

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Angioedema (swelling of tissue under the skin): difficulty breathing, or swollen face, hands, feet, lip, tongue, throat, or swelling of the digestive tract causing diarrhea, nausea, or vomiting.			**X**
Blood disorders (irregular white blood cell, platelet levels, and/or red blood cell levels): fever, weakness,		**X**	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
fatigue, flu-like symptoms, pale skin, shortness of breath, wheezing, infections, easy bruising, bleeding gums, nosebleeds, abdominal pain, rash, weight loss, rapid heartbeat, or yellowing of skin or eyes.			
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced sex drive, or thoughts of death or suicide.	**X**		
Gastrointestinal (GI) tract problems: black stools, weakness, dizziness, nausea, vomiting, stomach pain, constipation, or diarrhea.		**X**	
Heart problems: discomfort in the shoulder, arm, back, throat, jaw or teeth, pain or pressure in the chest, jaw, left arm or upper abdomen, fast-beating, fluttering pounding heart, skipping beats, beating too fast, pounding, heart attack, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, or abnormal heart rhythms.		**X**	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up).		**X**	
Kidney problems: increased urine amount or frequency, fatigue, nausea, vomiting, swelling, cramps, dry skin, itchy skin, loss of appetite, fever, or feeling thirsty.		**X**	
Liver problems: abdominal pain, fatigue, fever, itchiness, light-coloured stool, trouble thinking clearly, or yellowing of the skin or eyes.		**X**	
Nervous system disorders: increase in muscle tone, hard to stay asleep, burning, or prickling sensation, or loss of coordination.	**X**		
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart beat, nausea, vomiting, or tenderness when touching the		**X**	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
abdomen.			
Severe skin reactions (including Stevens-Johnson syndrome): increased sensitivity to light, blisters, redness, peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, fever, chills, headache, cough, body aches, or swollen glands.			**X**
Stroke (bleeding or blood clot in the brain): sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; or suddenly feeling dizzy or sudden severe headache without a known cause.			**X**
Unknown			
Allergic reactions: difficulty swallowing or breathing, wheezing, drop in blood pressure, nausea, vomiting, hives, rash, itching, swelling or irritating skin, or swelling of the face, lips, tongue or throat.			**X**
Eye problems: blurred vision, shape of objects appears distorted, blind spot that obstructs part of your vision, and temporary vision loss.	**X**		
Hyperkalemia (high amounts of potassium in the blood): palpitations, shortness of breath, chest pain, nausea, vomiting, diarrhea, weakness, or irregular heartbeat.		**X**	
Small bowel angioedema (swelling inside the small intestine)**:** stomach pain, nausea, vomiting, diarrhea, bloating, or feeling full quickly.		**X**	

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- Store BENAZEPRIL in the original package at room temperature (15°C to 30°C). It should be placed somewhere dry and out of direct light.
- The expiry date of this medicine is printed on the package label. Do not use the medicine after this date. If your healthcare professional tells you to stop taking BENAZEPRIL or you find that they have passed their expiry date, please return any left over medicine to your pharmacist.
- Keep out of reach and sight of children.

If you want more information about BENAZEPRIL:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc., 1165 Creditstone Road Unit #1, Vaughan, Ontario, L4K 4N7.

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