

# **PRODUCT MONOGRAPH**

**Pr** **BENAZEPRIL**

**Benazepril Hydrochloride**

**Tablets 5 mg, 10 mg and 20 mg**

**House Standard**

**Angiotensin Converting Enzyme Inhibitor**

**AA PHARMA INC.  
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<sup>Pr</sup>**BENAZEPRIL**

(benazepril hydrochloride)  
House Standard

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Nonmedicinal Ingredients</b>
oral	tablet / 5 mg, 10 mg and 20 mg	colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, red iron oxide (20 mg), titanium dioxide, yellow iron oxide (5 mg and 10 mg), and zinc stearate.

**INDICATIONS AND CLINICAL USE**

BENAZEPRIL (benazepril HCl) is indicated in the treatment of mild to moderate essential hypertension. It may be used alone or in association with thiazide diuretics.

In using BENAZEPRIL, consideration should be given to the risk of angioedema (see WARNINGS AND PRECAUTIONS). BENAZEPRIL should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

BENAZEPRIL can also be tried as an initial agent in those patients in whom use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of BENAZEPRIL 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 with antihypertensive agents other than thiazide diuretics have not been established.

**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.

### **Pediatrics (18 < years of age):**

Safety and effectiveness of BENAZEPRIL in children have not been established, therefore its use in this age group is not recommended.

### **CONTRAINDICATIONS**

BENAZEPRIL (benazepril HCl) is contraindicated in:

- Patients with known hypersensitivity to this product or any of its components. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**
- In patients with a history of angioedema with or without previous treatment with an ACE inhibitor.
- Pregnant and nursing women (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and Nursing Women**).
- 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 **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

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 <60ml/min/1.73m<sup>2</sup>) is contraindicated (see **WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS)** with ACEIs, ARBs or aliskiren).

### **WARNINGS AND PRECAUTIONS**

#### **Serious Warnings and Precautions**

**When used in pregnancy, angiotensin converting enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, BENAZEPRIL (benazepril hydrochloride) should be discontinued as soon as possible.**

#### **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<60ml/min/1.73m<sup>2</sup>). Therefore, the use of benazepril

hydrochloride in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ACEIs, 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.

### **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 **DRUG INTERACTIONS**).

### **Cardiovascular**

#### **Hypotension**

Occasionally, orthostatic hypotension has occurred after administration of benazepril hydrochloride usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see **ADVERSE REACTIONS**). Because of the potential fall in blood pressure in these patients, therapy with benazepril hydrochloride 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 is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

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

#### **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.

## **Ear/Nose/Throat**

### **Cough**

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

## **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.

Elevations of liver enzymes and/or serum bilirubin have been reported with benazepril hydrochloride (see ADVERSE REACTIONS). Should the patient receiving benazepril hydrochloride 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 should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. Benazepril hydrochloride 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. Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, benazepril hydrochloride should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

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 **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 **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

### **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) 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 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 (see **DRUG INTERACTIONS**).

### **Peri-Operative 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 produce hypotension,

benazepril 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 ACEIs – including benazepril hydrochloride – or of ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60ml/min/1.73m<sup>2</sup>) (see CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, 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 may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

*Use of BENAZEPRIL (benazepril HCl) should include appropriate assessment of renal function.*

### ***Special Populations***

#### **Pregnant Women:**

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, benazepril hydrochloride 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, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

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

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function, however,



limited experience with those procedures has not been associated with significant clinical benefit.

It is not known if benazepril hydrochloride can be removed from the body by hemodialysis.

### **Nursing Women:**

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is not recommended during breast-feeding.

### **Pediatrics (18< years of age):**

Safety and effectiveness of benazepril hydrochloride in children have not been established, therefore its use in this age group is not recommended.

### **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.

## **Monitoring and Laboratory Tests**

### **Neutropenia/Agranulocytosis**

Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Current experience with benazepril hydrochloride shows the incidence to be rare and a causal relationship to the administration of benazepril hydrochloride 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.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Benazepril hydrochloride has been evaluated for safety in over 6,000 hypertensive patients. Over 400 elderly patients have participated in controlled hypertension trials. Long-term safety has been assessed in more than 700 patients treated for 1 year or more. There was no increase in the incidence of adverse reactions in elderly patients given the same daily dose. 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 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%). Hypotension or postural dizziness was a cause for discontinuation of therapy in < 0.2% of patients treated with benazepril alone. Myocardial infarction and cerebral vascular accident occurred, possibly secondary to excessive hypotension in high risk patients (see **WARNINGS AND PRECAUTIONS**).

## Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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.

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 1 - Reported adverse reactions according to body systems**

	<b>Benazepril hydrochloride Patients (N=2004) (%)</b>
<b>Nervous System</b>	
Headache	10.2%
Dizziness	4.2%
Somnolence	1.1%
Vertigo	1.1%
<b>Respiratory</b>	
Symptoms of upper respiratory tract infection	5.4%
Increased cough	3.4%
Flu symptoms	1.2%
<b>Gastrointestinal</b>	
Nausea	2.5%
Abdominal pain	2.4%
Diarrhea	2.0%
Dyspepsia	1.2%
<b>Musculoskeletal</b>	
Musculoskeletal pain	2.6%
<b>Other</b>	
Fatigue	3.6%
Rhinitis	2.4%
Pharyngitis	1.7%
Back Pain	1.7%
Chest Pain	1.2%

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

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

<b>Body as Whole:</b>	asthenia
<b>Cardiovascular:</b>	excessive hypotension, angina pectoris, palpitations, myocardial infarction, cerebrovascular accident, arrhythmia.
<b>Digestive:</b>	constipation, gastritis, vomiting, flatulence, melena, abdominal pain, pancreatitis
<b>Musculoskeletal:</b>	arthritis, arthralgia, myalgia
<b>Nervous:</b>	anxiety, depression, hypertonia, insomnia, nervousness, paresthesia, incoordination, decreased libido
<b>Respiratory:</b>	dyspnea, asthma, bronchitis
<b>Dermatologic:</b>	apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, pemphigus, flushing, Stevens-Johnson Syndrome
<b>Special Senses:</b>	tinnitus, taste disorders
<b>Urogenital:</b>	impaired renal function, impotence, pollakiuria
<b>Hematologic:</b>	leucopenia, eosinophilia, hemolytic anemia and thrombocytopenia
<b>Allergic and immune reactions:</b>	angioedema, lip edema, face edema
<b>Liver:</b>	hepatitis (predominantly cholestatic), cholestatic jaundice

**Abnormal Hematologic and Clinical Chemistry Findings**

**Hyperkalemia (see WARNINGS AND PRECAUTIONS)**

**Creatinine, Blood Urea Nitrogen:** Increases in serum creatinine (> 150% of baseline) were observed in 2% of patients treated with benazepril hydrochloride 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 alone. These increases often reversed on continued therapy.

**Neutropenia:** Neutrophil counts of less than 1500/mm<sup>3</sup> occurred in 2% of patients treated with benazepril 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<sup>3</sup> and no patient developed a serious infection in association with a reduced neutrophil or WBC count. No patient treated with benazepril developed agranulocytosis (see WARNINGS AND PRECAUTIONS).

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

**Hepatic:** Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS AND PRECAUTIONS).

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

### Post-Market Adverse Drug Reactions

The following adverse events of unknown frequency have been reported during post-marketing use of benazepril: small bowel angioedema, anaphylactoid reactions, hyperkalemia, agranulocytosis, neutropenia, impaired vision (e.g. blurred vision, metamorphopsia, scotoma, and temporary vision loss) (see **WARNINGS AND PRECAUTIONS**).

## DRUG INTERACTIONS

### Overview

See **WARNINGS and PRECAUTIONS**, Dual Blockage of the Renin-Angiotensin System (RAS).

Benazepril is hydrolysed to the active metabolite benazeprilat, which inhibits the ACE and so 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. The possible or documented drug-drug interactions are tabulated below:

### Drug-Drug Interactions

**Table 2 - Established or Potential Drug-Drug Interactions for benazepril**

Proper name	Ref	Effect	Clinical comment
All Diuretics	C	Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may	The possibility of hypotensive effects after the first dose of benazepril hydrochloride can be minimized by either discontinuing the diuretic or

<b>Proper name</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical comment</b>
		occasionally experience an excessive reduction of blood pressure after initiation of therapy.	increasing the salt intake prior to initiation of treatment with benazepril hydrochloride. If it is not possible to discontinue the diuretic, the starting dose of benazepril hydrochloride should be reduced and the patient should be closely observed for several hours following initial dose and until blood pressure has stabilized (see <b>WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION</b> ).
<b>Agents Causing Renin Release</b>	CT	The antihypertensive effect of benazepril hydrochloride 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 with agents causing renin release cannot be avoided.
<b>Agents Increasing Serum Potassium</b>	CT, C	Since benazepril hydrochloride 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) 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.
<b>Agents Affecting Sympathetic Activity</b>	CT	Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. $\beta$ -adrenergic blocking agents add some further antihypertensive effect to benazepril hydrochloride.	Close monitoring of blood pressure and dose adjustment may be required if coadministration of benazepril hydrochloride with agents affecting sympathetic activity cannot be avoided.
<b>Dual blockade of the Renin-Angiotensin-System (RAS) with ACEIs, ARBs or aliskiren-containing drugs</b>	CT	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	The use of benazepril hydrochloride in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ACEIs, 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.

Proper name	Ref	Effect	Clinical comment
		moderate to severe renal impairment (GFR<60ml/min/1.73m <sup>2</sup> ).	
<b>Non steroidal anti-inflammatory drugs (NSAIDs)</b>	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 and no important changes in pharmacokinetic parameters occurred when single doses of benazepril hydrochloride were administered concomitantly with acetylsalicylic acid. The combination of non-steroidal anti-inflammatory drugs and ACE inhibitors, (including benazepril) can increase the risk of renal impairment and hyperkalaemia.	Monitoring of renal function and potassium level is recommended.
<b>Oral Anticoagulants</b>	CT	Multiple dose interaction studies failed to identify any 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 with warfarin or nicoumalone.	
<b>Lithium</b>	C	Increased lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors (including benazepril) 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.
<b>Drugs causing angioedema</b>	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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS 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 (eg. sacubitril/valsartan).  Concomitant treatment with a neprilysin inhibitor (eg. sacubitril/valsartan) is contraindicated.
<b>Other agents with antihypertensive</b>	CT	Benazepril hydrochloride may increase the hypotensive effect of	Dosages must be adjusted accordingly.

Proper name	Ref	Effect	Clinical comment
<b>properties</b>		other antihypertensive agents.	
<b>Hydrochlorothiazide, Chlorthalidone and Furosemide</b>	CT	The bioavailability of benazepril hydrochloride was not altered when single doses were administered concomitantly with the diuretics hydrochlorothiazide, chlorthalidone or furosemide.	
<b>Digoxin</b>	CT	In a single dose interaction study of benazepril hydrochloride with multiple doses of digoxin, no important changes <sup>1</sup> in pharmacokinetic parameters were observed.	
<b>Amlodipine/Nifedipine</b>	CT	Benazepril hydrochloride has been used concomitantly with the calcium channel blockers amlodipine and nifedipine, without evidence of clinically important adverse interactions.	
<b>Insulin/Oral anti-diabetics</b>	C	ACE inhibitors (including benazepril hydrochloride) may reduce insulin resistance. In isolated cases, such reduction may lead to hypoglycemic reactions in patients treated concomitantly with anti-diabetics.	Particularly close blood glucose monitoring is recommended. In case of persistent and/or severe hypoglycemia, dose adjustment or discontinuation of benazepril hydrochloride should be considered.
<b>Erythropoietin</b>	T	Patient responsiveness to erythropoietin may decrease when use concomitantly with ACE inhibitors (including benazepril).	
<b>Gold</b>	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 cannot be avoided.
<b>Probenecid</b>	CT	Probenecid pretreatment may enhance the pharmacodynamic response of ACE inhibitors.	Dose adjustment may be necessary.
<b>Other</b>	CT	In separate single or multiple dose pharmacokinetic interaction studies, the bioavailability of benazepril hydrochloride was not altered by coadministration with propranolol, naproxen, atenolol, nifedipine or cimetidine.	

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

<sup>1</sup>The mean C<sub>max</sub> of Benazeprilat was found to be 519 ± 89 and 484 ± 119 p mol/g and the mean AUC of Benazeprilat was found to be 2990 ± 446 and 2876 ± 442 pmol \*h/g upon administration of Benazepril alone and in combination with Digoxin, respectively. Similarly, the mean C<sub>max</sub> of Digoxin was found to be 1.43 ± 0.44 and 1.54 ± 0.62 p mol/g and the mean AUC of Digoxin was found to be 15.15 ± 5.40 and 14.69 ± 5.63 pmol \*h/g upon administration of Digoxin alone and in combination with Benazepril, respectively. No significant variation in C<sub>max</sub> and AUC of

Benazeprilat and Digoxin were observed when they were administered together.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

Dosage of BENAZEPRIL (benazepril hydrochloride) 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.

### **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.



## OVERDOSAGE

Although there is very limited experience of overdosage with benazepril hydrochloride 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 management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Benazepril is an angiotensin converting enzyme (ACE) inhibitor.

Benazepril, 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. Slight increases in serum potassium have been observed in some hypertensive patients treated with benazepril hydrochloride alone. Essentially no change in mean serum potassium was seen in patients treated with benazepril hydrochloride and a thiazide diuretic (see **WARNINGS AND PRECAUTIONS**).

Removal of inhibition of renin secretion by angiotensin II leads to increased plasma renin activity (due to removal of negative feedback of renin release).

ACE is identical to kininase II. Thus, benazepril 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 lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low renin hypertension. In particular, benazepril hydrochloride was antihypertensive in all races studied, although it was somewhat less effective in blacks than in nonblacks.

### **Pharmacodynamics**

Administration of benazepril hydrochloride 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 WARNINGS AND PRECAUTIONS).

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 was 10 mg. In studies comparing the same daily dose of benazepril hydrochloride 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 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.

Efficacy and safety appear to be the same for elderly (> 65 years of age) and younger adult patients given the same daily dosages.

### **Pharmacokinetics**

**Absorption:** Following oral administration of benazepril hydrochloride, 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 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 nonfasting 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 are approximately dose-proportional within the dosage range (10 to 40 mg).

**Metabolism:** Benazepril is almost completely metabolized to benazeprilat, and to the glucuronide conjugates of benazepril and benazeprilat.

**Excretion:** 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**

**Hepatic Dysfunction:** In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered.

**Renal Insufficiency:** The disposition of benazepril 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 **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of benazepril and benazeprilat do not appear to be influenced by age.

### **STORAGE AND STABILITY**

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

### **SPECIAL HANDLING INSTRUCTIONS**

Not applicable

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

In addition to the active ingredient, benazepril hydrochloride, each film-coated tablet also contains 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.

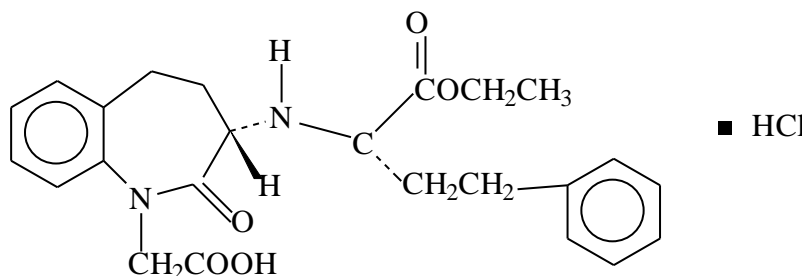
BENAZEPRIL 20 mg Tablets: Each light pink, round shaped, unscored film-coated tablet, plain on one side and engraved "BE" over "20" on the other side contains 20 mg of benazepril hydrochloride. Available in bottles of 100.

## PART II: SCIENTIFIC INFORMATION

### 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-1H-1-(3S)-benzazepine-1-acetic acid monohydrochloride
Molecular Formula:	C <sub>24</sub> H <sub>28</sub> N <sub>2</sub> O <sub>5</sub> •HCl
Molecular Weight:	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

## CLINICAL TRIALS

### 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<sup>®</sup> (Novartis Pharmaceuticals Canada Inc.) tablets. The results from measured data are summarized as follows:

### Summary Table of the Comparative Bioavailability Data – 5 mg Strength

Benazepril (2 x 5 mg) From Measured Data <b>Uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV%)				
Parameter	Benazepril§	Lotensin <sup>®</sup> †	% Ratio of Geometric Means**	90% Confidence interval**
AUC <sub>T</sub> (ng•hr/mL)	193 201 (27)	204 211 (27)	94.7	88.1 – 102
AUC <sub>I</sub> (ng•hr/mL)	195 202 (27)	206 213 (27)	94.7	88.1 – 102
C <sub>max</sub> (ng/mL)	250 259 (26)	260 269 (25)	96.3	84.2 - 110
T <sub>max</sub> (hr)*	0.40 (32)	0.45 (28)		
t <sub>1/2</sub> (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<sup>®</sup> 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<sup>®</sup> (Novartis Pharmaceuticals Canada Inc.) tablets. The results from measured data are summarized as follows:

### Summary Table of the Comparative Bioavailability Data – 20 mg Strength

Benazepril (1 x 20 mg) From Measured Data <b>Uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV%) Based on Benazepril				
Parameter	Benazepril§	Lotensin <sup>®</sup> †	% Ratio of Geometric Means**	90% Confidence interval**
AUC <sub>T</sub> (ng•hr/mL)	216 231 (35)	209 219 (30)	103.3	96.8 – 110.2
AUC <sub>I</sub> (ng•hr/mL)	219 233 (35)	211 221 (30)	103.3	96.9 – 110.1
C <sub>max</sub> (ng/mL)	311 336 (39)	293 307 (30)	104.2	92.3 – 117.5
T <sub>max</sub> (hr)*	0.43 (28)	0.47 (27)		
t <sub>1/2</sub> (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 <sup>®</sup> is manufactured by Novartis Pharmaceuticals Canada Inc., and was purchased in Canada				

## **DETAILED PHARMACOLOGY**

Benazepril HCl exhibited antihypertensive activity in spontaneously hypertensive and renal hypertensive rats in oral doses ranging from 0.1 to 10 mg/kg. Antihypertensive efficacy was evident in renal hypertensive dogs receiving 3.0 mg/kg P.O. of benazepril HCl. In these rat and dog models, blood pressure reductions were detected as early as 1.5 to 2 hours after the first dose and activity persisted up to 24 hours after dosage. The antihypertensive efficacy gradually increased up to the second or third day of dosage when benazepril was given once daily. In the



hypertensive rat studies, no tolerance to the antihypertensive action was evident with daily dosage continued up to 4 weeks. There was a gradual return to initial levels when treatment was discontinued.

In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate.

In spontaneous hypertensive rats, blood flow to various tissue beds (kidney, heart, and selected brain and gastrointestinal regions) was unaffected by benazepril.

Characterization of the ACE inhibitory activity of benazepril and benazeprilat was provided directly by studies with the isolated enzyme or tissues containing the enzyme. Indirect evidence of enzyme inhibition was provided by prevention of the effects of angiotensin I on contraction of isolated smooth muscle preparations and on pressor responses of rats and dogs.

In a study in dogs, benazepril was shown to potentiate the hypotensive effect of an injection of bradykinin, the degradation of which is catalyzed by ACE.

In animal studies, benazepril 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.

Benazepril passes the blood-brain barrier only to an extremely low extent, as evidenced by studies in rats with <sup>14</sup>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 HCl 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. Some placental passage occurred when the drug was administered to pregnant rats.

## TOXICOLOGY

**Table 3 - Acute Toxicity**

Species	Route	Sex	LD <sub>50</sub> (mg/kg)
Mouse	P.O.	♂	3350-4019
		♀	3160
	I.V.	♂	562
		♀	537
	S.C.	♂	> 3200
		♀	> 3600
Rat	P.O.	♂	> 5000

Species	Route	Sex	LD <sub>50</sub> (mg/kg)
	I.V.	♂ ♀ +	432 483
	S.C.	♂ ♀ +	3400 4200

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  $\geq 250$  mg/kg and  $\geq 500$  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.

**Table 4 - Long-Term Toxicity Studies of Benazepril**

Species	Duration	Sex	Route	Daily doses	Results
Rat	13 wks	♂ & ♀	P.O.	0, 1, 10, 100, 1000 mg/kg	Salivation at high dose. ↓ food consumption & body weight gain in ♂ $\geq 10$ mg/kg, ♀ $\geq 100$ mg/kg. Urinary effects in ♂ $\geq 10$ mg/kg. Anemia in high dose ♂ + ♀. ↑ inorganic phosphorous in high dose ♂ and ♀ & ↑ BUN in high dose ♂. ↑ K <sup>+</sup> in ♂ at doses $\geq 10$ mg/kg. ↓ total protein & albumin in ♂ at doses $\geq 100$ mg/kg. ↓ absolute and relative weights of liver, heart and thyroid in ♂ and ↑ relative kidney weights in ♀ at doses $\geq 100$ mg/kg. ↑ PAS & granules in JG-cells $\geq 10$ mg/kg. Most effects reversible after 5 weeks. No gross changes attributed to treatment at autopsy.
Rat	6 months	♂ & ♀	P.O.	0, 15, 50, 150 mg/kg	↓ body weight gain in ♂ $\geq 50$ mg/kg. ↑ BUN, ↓ ACE at doses $\geq 50$ mg/kg. Organ weight effects (heart & liver ↓; kidney ↑) at all dose levels. ↑ serum K <sup>+</sup> in 150 mg/kg ♂. Focal tubular cortical renal lesions in high dose ♂ & ♀.
Rat	52 weeks	♂ & ♀	Diet	0, 10, 50, 250 mg/kg	No compound related mortalities. ↓ erythroid parameters $\geq 50$ mg/kg. ↑ in mean percent reticulocytes in ♀ at

Species	Duration	Sex	Route	Daily doses	Results
					250 mg/kg. ↑ in mean serum K <sup>+</sup> in ♂ at ≥ 50 mg/kg and Cl <sup>-</sup> in ♂ or ♀ at ≥ 10 mg/kg. ↑ BUN at ≥ 50 mg/kg. At all doses: ↓ food consumption & body weight gain, JG-cell & arteriolar hypertrophy, and ↓ senile nephropathy. ↓ in mean absolute and/or relative heart weight. ↓ kidney and liver weights in all ♂ and high dose ♀. ↑ prostate weights in ♂ at ≥ 50 mg/kg and thymus at ≥ 250 mg/kg.
Dog	13 weeks	♂ & ♀	P.O. (gavage)	0, 1, 10, 30, 100 → 150 mg/kg (dose ↑ on test day 50)	No mortalities and related compound effects only at high dose. Emesis and anorexia. ↑ body weight gain ♂. ↑ SGPT, BUN, creatinine. ↓ heart weights without ECG or microscopic changes. No microscopic pathological changes.
Dog	12 months	♂ & ♀	P.O. (capsule)	0, 15, 50, 150 mg/kg	No mortality and no clinical signs related to compound. ↓ food consumption & body weight gain in ♂ ≥ 50 mg/kg. ↑ BUN and erythroid parameters at some time points at ≥ 50 mg/kg. ↑ HR at ≥ 150 mg/kg. Splenic hemosiderosis and slight renal cortical tubular basophilia and interstitial inflammation at 150 mg/kg. JG and arteriolar hypertrophy at all doses. All effects showed reversibility after 1 month.

### Reproduction and Teratology Studies

No adverse effects on reproductive performance were observed in male and female rats treated with 50 to 500 mg/kg/day of benazepril HCl during gestational days 6 through 15 or from 14 days prepartum to 21 days postpartum.

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, 150 mg/kg/day and 5 mg/kg/day, 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 respectively. No embryotoxic or teratogenic effects of benazepril HCl 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).

### **Carcinogenicity Studies**

No evidence of a tumorigenic effect was seen when benazepril HCl was administered for 104 weeks to rats at a dose of up to 150 mg/kg/day. No evidence of carcinogenicity was seen when benazepril was administered for up to 104 weeks to mice at the same dose.

### **Mutagenicity Studies**

Benazepril was not mutagenic when tested in the Ames microbial mutagen test with or without metabolic activation. The following genotoxicity studies with benazepril 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.

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Product Monograph - Lotensin<sup>®</sup> (benazepril hydrochloride). Novartis Pharmaceuticals Canada Inc. Date of Preparation: September 20, 2018. Submission Control No: 216946.

**PART III: CONSUMER INFORMATION**

**Pr BENAZEPRIL**

**Benazepril Hydrochloride tablets  
House Standard**

**Read this carefully before you start taking BENAZEPRIL and each time you get a refill. This leaflet is a summary and will not tell you everything about BENAZEPRIL. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about BENAZEPRIL.**

**ABOUT THIS MEDICATION**

**What the medication is used for:**

BENAZEPRIL lowers high blood pressure.

**What it does:**

BENAZEPRIL is an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in ‘-PRIL’.

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking BENAZEPRIL regularly even if you feel fine.

**When it should not be used:**

Do not take BENAZEPRIL if you:

- Are allergic to BENAZEPRIL or to any nonmedicinal ingredient in the formulation.
- 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 any other medication, including medications for blood pressure, or without a known cause. Be sure to tell your doctor, nurse, or pharmacist 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 pregnant or intend to become pregnant. Taking BENAZEPRIL during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. BENAZEPRIL passes into breast milk.
- Are already taking a blood pressure- lowering medicine that contains aliskiren (such as RASILEZ) and you have diabetes or kidney disease.

- Are taking other medicines that contain a neprilysin inhibitor (e.g. sacubitril/valsartan).

**What the medicinal ingredient is:**

Benazepril hydrochloride.

**What the important nonmedicinal ingredients are:**

BENAZEPRIL tablets contain the following inactive 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.

**What dosage forms it comes in:**

BENAZEPRIL is available as 5 mg, 10 mg and 20 mg tablets.

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions-Pregnancy**

**BENAZEPRIL should not be used during pregnancy. If you discover that you are pregnant while taking BENAZEPRIL, stop the medication and contact your doctor, nurse, or pharmacist as soon as possible.**

**Before taking BENAZEPRIL, talk to your doctor, nurse or pharmacist if you:**

- Are allergic to any drug used to lower blood pressure.
- Have recently received or are planning to get allergy shots for bee or wasp stings. Your doctor 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.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure,
- Have liver or kidney disease.
- Have diabetes.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are on dialysis.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of “water pill”),
- Are on a low-salt diet,
- Are receiving gold (sodium aurothiomalate) injections.
- Are less than 18 years old.

## IMPORTANT: PLEASE READ

- Have collagen vascular diseases. Collagen vascular diseases are (diseases in which the body reacts against its own tissues, often causing joint pain and inflammation). Examples are systemic lupus erythematosus or scleroderma.
- Are taking a medicine that contains aliskiren, such as RASILEZ, used to lower high blood pressure. The combination with BENAZEPRIL is not recommended.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in “-SARTAN”.
- Are taking medicine to treat some cancer and non-cancerous growths associated with genetic disorders ((e.g. temsirolimus, sirolimus, everolimus).

You may become sensitive to the sun while taking BENAZEPRIL. 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 doctor or dentist that you are taking BENAZEPRIL.

**Driving and using machines:** Before you perform tasks which may require special attention, wait until you know how you respond to BENAZEPRIL. Dizziness, lightheadedness, or fainting can occur. Take care especially after the first dose and when the dose is increased.

### INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with BENAZEPRIL:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of “water pill”).
- Alcohol as it may make blood pressure fall more and/or increase the possibility of dizziness or fainting.
- Antidiabetic drugs, including insulin, oral medicines and dipeptidyl peptide-IV inhibitors.
- Gout medications, including allopurinol and probenecid.
- Lithium used to treat bipolar disease and other psychological conditions.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples

include ibuprofen, naproxen, indomethacin and celecoxib.

- Other blood pressure lowering drugs, including diuretics (“water pills”), angiotensin receptor blockers ARBs or aliskiren-containing products (e.g. RASILEZ).
- Cyclosporine, an immunosuppressant medicine used in transplanted patients to reduce the risk of organ rejection.
- Heparin, an anticoagulant medicine used to prevent or treat blood clots.
- Erythropoietin, a medicine used to regulate the production of red blood cells.
- Gold for the treatment of rheumatoid arthritis.
- Medicine used to treat some cancers and also some non-cancerous growths associated with a genetic disorder (e.g. temsirolimus, sirolimus, everolimus)

### PROPER USE OF THIS MEDICATION

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

You can take BENAZEPRIL before, during or after a meal since food will not decrease its effectiveness. Swallow your tablet with a glass of water.

The dose of BENAZEPRIL must be individualized. Your doctor will prescribe the lowest possible dose for your needs, to be taken once or twice a day. Your doctor will tell you exactly how many tablets of BENAZEPRIL to take. Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose. Do not exceed the recommended dose. Never change the dose unless told to do so.

#### Usual Adult Dose:

Recommended Initial Dose: 10 mg a day.

Usual Maintenance Dose: 20 mg a day.

Maximum Dose: 40 mg a day.

In patients with severe kidney disease:

Recommended Initial Dose: 5 mg a day.

#### Overdose:

If you think you have taken too much BENAZEPRIL contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.



**Missed Dose:**

If you miss 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 take a double dose on the next day to make up for the forgotten tablet(s).

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Side effects may include:

- dizziness;
- drowsiness, fatigue, weakness;
- cough (dry, non-productive, mainly at night, continuing);
- sore throat and throat irritation;
- headache;
- abdominal pain; pain in your muscles, back or bones,
- rash, itching, increased sensitivity of the skin to sun, flushing;
- diarrhea, constipation, vomiting, nausea, stomach upset;
- numbness or tingling in the hands, feet or lips;
- ringing in the ears;
- loss of taste;
- erectile dysfunction;

**If any of these affects you severely, tell your doctor, nurse or pharmacist.**

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

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
<b>Common</b>	<b>Increased levels of potassium in the blood:</b> irregular heartbeat, muscle weakness and generally feeling unwell		√	

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	<b>Decreased White Blood Cells:</b> infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
<b>Uncommon</b>	<b>Electrolyte Imbalance:</b> weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
	<b>Allergic Reactions, (Angiodema):</b> Rash, hives, swelling of the face, eyes, lips or tongue, throat, arms or legs, or trouble swallowing or breathing			√
	<b>Low Blood Pressure:</b> Dizziness, light-headedness, fainting. May occur when you go from lying or sitting to standing up.	√		
	<b>Inflammation of the Pancreas:</b> abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		√	

**IMPORTANT: PLEASE READ**

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
<b>Liver Disorder:</b> Yellowing of the skin or eyes, abdominal pain, nausea, vomiting, loss of appetite, dark urine.		√	
<b>Kidney Disorder:</b> change in frequency of urination, nausea, vomiting, swelling of extremities fatigue		√	
<b>Stroke:</b> numbness, tingling, weakness on one side of your body, vision changes, trouble speaking, walking or with balance, confusion, and severe headache			√
<b>Depression:</b> Sad mood, nervousness, sleep problems, tiredness	√		
<b>Respiratory Problems:</b> Shortness of breath, trouble breathing, wheezing		√	
<b>Heart Attack:</b> Sudden crushing chest pain, fast or irregular heartbeat, shortness of breath			√

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
<b>Stevens-Johnson Syndrome:</b> Rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever			√
<b>Anemia:</b> fatigue, loss of energy, weakness, shortness of breath		√	
<b>Decreased Platelets:</b> bruising, spontaneous bleeding, fatigue and weakness		√	
<b>Hypoglycemia:</b> (low blood sugars in diabetic patients): Nervousness, sweating, trembling, weakness, palpitations	√		
<b>Vision problems:</b> Blurred or decreased vision, temporary loss of vision, seeing in a distorted manner			√

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

**HOW TO STORE IT**

All medicines should be kept out of the reach of children. BENAZEPRIL should be stored in its original package at room temperature, in a dry place 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 doctor 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.

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

**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.*

**MORE INFORMATION**

**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 this Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>). Find the Consumer Information on the manufacturer’s website (<http://www.apotex.ca/products>), or by calling 1-800-667-4708.

This leaflet was prepared by AA Pharma Inc.

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