Product Monograph

PrLOTENSIN*

(benazepril hydrochloride)

5 mg, 10 mg and 20 mg tablets

Angiotensin Converting Enzyme Inhibitor

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DATE OF REVISION:
July 12, 2011

Control # 146592

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Pharmacological Classification
Angiotensin Converting Enzyme Inhibitor

Action And Clinical Pharmacology

LOTENSIN* (benazepril HCl) is an angiotensin converting enzyme (ACE) inhibitor which is used in the treatment of hypertension.

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 LOTENSIN* alone. Essentially no change in mean serum potassium was seen in patients treated with LOTENSIN* and a thiazide diuretic (**see 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 LOTENSIN* 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, LOTENSIN* was antihypertensive inall races studied, although it was somewhat less effective in blacks than in nonblacks.

Pharmacokinetics and Metabolism

Following oral administration of LOTENSIN*, peak plasma concentrations of benazepril are reached within 0.5-1.0 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 1-2 hours after drug intake in the fasting state and 2-4 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. Benazeprilat is eliminated predominantly by renal excretion and has an effective accumulation half-life of 10-11 hours. The serum protein binding of benazepril is about 97%, and that of benazeprilat about 95%.

Benazepril is almost completely metabolized to benazeprilat, and to the glucuronide conjugates of benazepril and benazeprilat. Only trace amounts of an administered dose of LOTENSIN* 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 (10-40 mg).

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**).

In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. The pharmacokinetics of benazepril and benazeprilat do not appear to be influenced by age.

Pharmacodynamics

Administration of LOTENSIN* 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**).

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 2-4 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 LOTENSIN* was 10 mg. In studies comparing the same daily dose of LOTENSIN* 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 1-2 weeks. Abrupt withdrawal of LOTENSIN* has not been associated with a rapid increase in blood pressure.

When LOTENSIN* 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.

Indications And Clinical Use

LOTENSIN* (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 LOTENSIN*, consideration should be given to the risk of angioedema (**see Warnings**). LOTENSIN* 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.

LOTENSIN* 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 LOTENSIN* 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 LOTENSIN* with antihypertensive agents other than thiazide diuretics have not been established.

Contraindications

LOTENSIN* (benazepril HCl) is contraindicated in patients with known hypersensitivity to this product or any of its components and in patients with a history of angioedema with or without previous treatment with an ACE inhibitor. LOTENSIN* is contraindicated during pregnancy (see Warnings, Serious Warnings and Precautions).

Warnings

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, LOTENSIN* should be discontinued as soon as possible.

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 LOTENSIN*) may experience a variety of adverse reactions, some of them serious.

Angioedema

Angioedema has been reported in patients with ACE inhibitors, including LOTENSIN* (benazepril HCl). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, LOTENSIN* 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 heritage 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**).

Hypotension

Occasionally, orthostatic hypotension has occurred after administration of LOTENSIN* 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 LOTENSIN* should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of LOTENSIN* 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 LOTENSIN* and/or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis

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

Pregnant Women

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, LOTENSIN* 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 LOTENSIN* can be removed from the body by hemodialysis.

Animal Data: 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 LOTENSIN* 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).

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.

Precautions

Renal Impairment

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

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

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.

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**).

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.

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.

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 LOTENSIN* (**see Adverse Reactions**). Should the patient receiving LOTENSIN* 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 LOTENSIN* should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. LOTENSIN* 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.

Cough

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

Pediatric Use

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

Use in the Elderly

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.

Drug Interactions

Concomitant Diuretic Therapy

Patients concomitantly taking ACE inhibitors and diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy. The possibility of hypotensive effects after the first dose of LOTENSIN* can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with LOTENSIN*. If it is not possible to discontinue the diuretic, the starting dose of LOTENSIN* should be reduced and the patient should be closely observed for several hours following initial dose and until blood pressure has stabilized (**see Warnings and Dosage And Administration**).

Agents Causing Renin Release

The antihypertensive effect of LOTENSIN* is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Agents Increasing Serum Potassium

Since LOTENSIN* 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 and frequent monitoring of serum potassium, since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.

Agents Affecting Sympathetic Activity

Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. β-adrenergic blocking agents add some further antihypertensive effect to LOTENSIN*.

Non steroidal anti-inflammatory drugs (NSAIDs)

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 LOTENSIN* and no important changes in pharmacokinetic parameters occurred when single doses of LOTENSIN* 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. Therefore, monitoring of renal function and potassium level is recommended.

Oral Anticoagulants

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.

Lithium

Increased lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors (including LOTENSIN*) 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.

Dipeptidyl peptidase-IV inhibitors

The risk of angioedema may be increased in patients receiving co-administration of ACE inhibitors and dipeptidyl peptidase-IV inhibitors.

Other agents with antihypertensive properties

LOTENSIN* may increase the hypotensive effect of other antihypertensive agents. Dosages must be adjusted accordingly.

Hydrochlorothiazide, Chlorthalidone and Furosemide

The bioavailability of LOTENSIN* was not altered when single doses were administered concomitantly with the diuretics hydrochlorothiazide, chlorthalidone or furosemide.

Digoxin

In a single dose interaction study of LOTENSIN* with multiple doses of digoxin, no important changes in pharmacokinetic parameters were observed.

Amlodipine/Nifedipine

LOTENSIN* has been used concomitantly with the calcium channel blockers amlodipine and nifedipine, without evidence of clinically important adverse interactions.

Insulin/Oral anti-diabetics

ACE inhibitors (including LOTENSIN*) 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.

Erythropoietin

Patient responsiveness to erythropoietin may decrease when use concomitantly with ACE inhibitors (including benazepril).

Gold

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.

Probenecid

Probenecid pretreatment may enhance the pharmacodynamic response of ACE inhibitors. Dose adjustment may be necessary.

Other

In separate single or multiple dose pharmacokinetic interaction studies, the bioavailability of LOTENSIN* was not altered by coadministration with propranolol, naproxen, atenolol, nifedipine or cimetidine.

Adverse Reactions

LOTENSIN* (benazepril HCl) 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 LOTENSIN* 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**).

The most frequent clinical adverse reactions in placebo-controlled clinical trials with LOTENSIN* 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 LOTENSIN*.

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

Body System		Patients (N=2004)
Nervous System	Headache	10.2%
	Dizziness	4.2%
	Somnolence	1.1%
	Vertigo	1.1%
Respiratory	Symptoms of upper respiratory tract infection	5.4%
	Increased cough	3.4%
	Flu symptoms	1.2%
Gastrointestinal	Nausea	2.5%
	Abdominal pain	2.4%
	Diarrhea	2.0%
	Dyspepsia	1.2%
Musculoskeletal	Musculoskeletal pain	2.6%
Other	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 LOTENSIN* in controlled and uncontrolled clinical trials, and postmarketing experience, are listed below by body system:

Incidence less than 1%

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

Abnormal Laboratory Findings

Hyperkalemia (see Precautions)

Creatinine, Blood Urea Nitrogen: Increases in serum creatinine (> 150% of baseline) were observed in 2% of patients treated with LOTENSIN* 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 LOTENSIN* 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 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 developed agranulocytosis **(see Warnings)**.

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

Hepatic: Elevations of liver enzymes and/or serum bilirubin have occurred (**see 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, agranulacytosis, neutropenia, impaired vision (e.g. blurred vision, metamorphopsia, scotoma, and temporary vision loss)(**see Warnings**).

Symptoms And Treatment Of Overdosage

Although there is very limited experience of overdosage with LOTENSIN*, 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.

Dosage And Administration

Dosage of LOTENSIN* (benazepril HCl) 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 LOTENSIN* may need to be adjusted.

Monotherapy: The recommended initial dose of LOTENSIN* 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 LOTENSIN* 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.

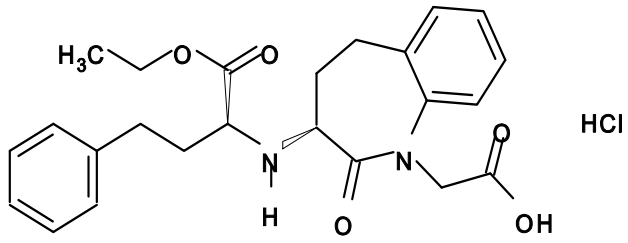
If blood pressure is not controlled with LOTENSIN* alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of LOTENSIN*.

Concomitant Diuretic Therapy: Orthostatic hypotension occasionally may occur following the initial dose of LOTENSIN* 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 LOTENSIN* 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. 2-3 days) prior to LOTENSIN* initiation or a reduction of the initial dose of LOTENSIN* in order to avoid excessive hypotension. If the diuretic cannot be discontinued, an initial dose of 5 mg LOTENSIN* should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of LOTENSIN* should subsequently be titrated (as described above) to the optimal response. Volume and/or salt depletion should be corrected before starting therapy with LOTENSIN*.

Dosage Adjustment in Renal Impairment: The usual dose of LOTENSIN* 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 LOTENSIN* can be increased.

Pharmaceutical Information

Drug Substance



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: $C_{24}H_{28}N_2O_5 \times HCl$

Molecular Weight: 460.96

Description: Practically odourless, white to off-white crystalline powder.

Solubility: Freely soluble in methanol and ethanol, soluble in water and phosphate buffer (pH 7), slightly soluble in dichloromethane and ethyl acetate, practically insoluble in cyclohexane.

pKa: 3.1 and 5.3 (when in water)

Melting Point 180.5-181.6°C.

Composition

LOTENSIN* 5 mg, 10 mg and 20 mg film-coated tablets also contain cellulose compounds, colloidal silicon dioxide, corn starch, hydrogenated castor oil, iron oxide, lactose, polyethylene glycol, crospovidone, talc and titanium dioxide.

Stability and Storage Recommendations

Protect from heat (i.e., store at 15°C - 30°C) and humidity.
LOTENSIN* must be kept out of reach of children.

Availability Of Dosage Forms

PrLOTENSIN* 5 mg Tablets

Light yellow, ovaloid, slightly biconvex, film-coated tablets. One side is imprinted **LV**, the other **CG** with a score on both sides.

Available in blister packages of 28 tablets.

PrLOTENSIN* 10 mg Tablets

Dark yellow, ovaloid, slightly biconvex, film-coated tablets. Fully bisected on both sides. One side is engraved **CG**, the other **HO**.

Available in blister packages of 28 tablets.

PrLOTENSIN* 20 mg Tablets

Light orange, round, slightly biconvex, film-coated tablets, with bevelled edges.

Available in blister packages of 28 tablets.

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 ^{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 3-4.5 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

Acute Toxicity

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

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 ♂ ≥ 10 mg/kg, ♀ ≥ 100 mg/kg. Urinary effects in ♂ ≥ 10 mg/kg. Anemia in high dose ♂ + ♀. ↑ inorganic phosphorous in high dose ♂ and ♀ & ↑ BUN in high dose ♂. ↑ K^+ in ♂ at doses ≥ 10 mg/kg. ↓ total protein & albumin in ♂ at doses ≥ 100 mg/kg. ↓ absolute and relative weights of liver, heart and thyroid in ♂ and ↑ relative kidney weights in ♀ at doses ≥ 100 mg/kg. ↑ PAS & granules in JG-cells ≥ 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 ♂ ≥ 50 mg/kg. ↑ BUN, ↓ ACE at doses ≥ 50 mg/kg. Organ weight effects (heart & liver ↓; kidney ↑) at all dose levels. ↑ serum K^+ 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 ≥ 50 mg/kg. ↑ in mean percent reticulocytes in ♀ at 250 mg/kg. ↑in mean serum K^+ in ♂ at ≥ 50 mg/kg and Cl^- 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 premating 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 ³ 250 mg/kg/day. Maternal toxicity with mortality occurred in rabbits at doses of 0.1 mg/kg/day or more.

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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Part III : CONSUMER INFORMATION

[Pr]LOTENSIN*
benapepril hydrochlororide

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

ABOUT THIS MEDICATION

What the medication is used for:
LOTENSIN* is a medication that helps lower high blood pressure (hypertension).

High blood pressure increases the workload of the heart and arteries. If this condition continues for a long time, damage to the blood vessels of the brain, heart, and kidneys can occur, and may eventually result in a stroke, heart failure or kidney failure. High blood pressure also increases the risk of heart attacks. Reducing your blood pressure decreases your risk of developing these illnesses.

What it does:
LOTENSIN* belongs to a class of drugs known as Angiotensin **C**onverting **E**nzyme (ACE) inhibitors. LOTENSIN* helps to control high blood pressure by preventing your body from producing a substance (angiotensin) that increases blood pressure.

When it should not be used:
You should not take LOTENSIN* if:
- you are allergic (hypersensitive) to LOTENSIN* or any of the other nonmedicinal ingredients of LOTENSIN* listed in this leaflet.
- you experienced a severe allergic reaction called angioedema (swelling of the face, lips, tongue, or throat, or had sudden difficulty breathing or swallowing) while taking an ACE inhibitor or any other medication, including medications for blood pressure
- you have been diagnosed with hereditary angioedema or idiopathic angioedema (angioedema of unknown cause).
- you are pregnant or plan to become pregnant.
- If you have severe lactose intolerance. LOTENSIN* contains lactose (milk sugar).

LOTENSIN* is not recommended for use in patients under 18 years of age.

What the medicinal ingredient is:
Benazepril hydrochloride.

What the nonmedicinal ingredients are:
Cellulose compounds, colloidal silicon dioxide, corn starch, crospovidone, hydrogenated castor oil, iron oxide, lactose, polyethylene glycol, talc and titanium dioxide.

What dosage forms it comes in:
Film-coated tablets 5 mg , 10 mg and 20 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
LOTENSIN* should not be used during pregnancy. If you discover that you are pregnant while taking **LOTENSIN***, stop the medication and please contact your physician as soon as possible.

BEFORE you use LOTENSIN* talk to your doctor or pharmacist if:
- you have liver disease, serious kidney disease, heart or vascular disease;
- you have a heart valve disorder.
- you are on a salt restricted diet;
- you are already taking another medicine to lower blood pressure;
- you are about to have an operation (including dental surgery) or emergency treatment;
- you are suffering from vomiting or diarrhea or excessive sweating;
- you are about to receive Hymenoptera venom treatment (a venom used to test or treat allergy to insect stings);
- you are about to have, or are having, dialysis;
- you are treated for hyperkalaemia (too much potassium in the blood);
- you have diabetes. LOTENSIN* can lower your blood sugar levels when taken with your diabetes medicine. Frequent blood glucose monitoring is recommended;
- you have a collagen vascular diseases **(**diverse group of diseases in which the body reacts against its own tissues, often causing joint pain and inflammation**),** such as systemic lupus erythematosus or scleroderma;
- you are breast-feeding, LOTENSIN* passes into the breast milk;
- if you have severe lactose intolerance, LOTENSIN* contains lactose (milk sugar).

If you experience any allergic reaction with symptoms such as swelling mainly of the face and throat (angioedema), **stop taking LOTENSIN* and contact your doctor straight away.**

Do not use salt substitutes containing potassium to flavour food without first consulting your doctor.

Taking **LOTENSIN*** during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant while taking **LOTENSIN***, stop the medication and report to your doctor as soon as possible.

Ask your doctor or pharmacist for advice before taking any medicine.

Make sure you know how you react to LOTENSIN before you drive, use machines or do other tasks that require you to be alert.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any medicines you are taking or have recently taken, including prescription medications (the ones your doctor writes for you) and over-the-counter medications (the ones you buy in the drugstore, like cold or allergy medicines), or natural health products (herbal medicines).

Drugs that may interact with LOTENSIN* include:

- medicines used to lower blood pressure, especially diuretics (water pills);
- lithium, a medicine used to treat some psychological conditions;
- potassium-containing medicines, potassium supplements or salt substitutes containing potassium;
- 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;
- indomethacin and other non-steroidal anti-inflammatory agents, medicines used to relieve pain and inflammation;
- insulin or oral antidiabetics, medicines that help a person with diabetes to control their level of glucose (sugar) in the blood;
- erythropoietin, a medicine used to regulate the production of red blood cells;
- gold for the treatment of rheumatoid arthritis;
- probenecid, a medicine used to treat gout and hyperuricemia;

Avoid alcohol until you have discussed the matter with your doctor. Alcohol may make blood pressure fall more and/or increase the possibility of dizziness or fainting.

PROPER USE OF THIS MEDICATION

Remember that this medicine does not cure your high blood pressure; it only may help to control it. Therefore, if you want to lower your blood pressure and keep it down, you must continue to take LOTENSIN* as directed.
Patients who have high blood pressure often do not notice any signs or symptoms of this condition. Indeed, many may feel quite normal for a long time. So even though you are feeling well, your health may be getting worse. This makes it all the more important for you to continue your treatment program and to keep your appointments with your doctor.

Usual dose:
The usual recommended initial dose is 10 mg a day. The usual maintenance dose is 20 mg a day. The maximum dose is 40 mg a day. Always follow your doctor's instructions because the dose of LOTENSIN should be individualized.

In general, treatment is started with the smallest dose and the dosage is then increased gradually. 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 LOTENSIN* 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.

You can take your LOTENSIN* before, during or after a meal since food will not decrease its effectiveness. Swallow your tablet with a glass of water. To help you to remember to take your medicine, try to take it at the same time each day.
This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

Overdose:

In case of drug overdose, contact a health care practitioner, 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

Like all medicines, LOTENSIN* may cause unwanted side effects in some people. The following side effects have been reported with patients taking LOTENSIN*:

- cough (dry, non-productive, mainly at night, continuing);
- pharyngitis sore throat and throat irritation (possible signs of upper respiratory tract infections);
- headache;
- itching, increased sensitivity of the skin to sun, flushing;
- diarrhea, constipation, vomiting, nausea, stomach upset ;
- numbness or tingling in the hands, feet or lips;
- abnormal kidney function blood test results, increased frequency of urination;
- ringing in the ears;
- loss of taste;
- erectile dysfunction;

Your doctor should take blood tests before starting LOTENSIN*. They will monitor the number of infection fighting white blood cells. Your doctor should continue to monitor your blood for as long as you are being treated.

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 emergency medical attention
		Only if severe	In all cases	
Common	**Hyperkalemia:** High potassium in the blood which may cause muscle weakness and heart problems		✓	
Rare	**Angioedema:** Swelling of the face, eyes, lips or tongue, arms or legs, or trouble swallowing or breathing			✓
	Heart Disorder: Sudden and oppressive chest pain, irregular heart beat , fast heartbeat, shortness of breath			✓
	Rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever			✓
	Inflamed Pancreas: Abdominal pain with nausea, vomiting, fever		✓	
	Liver Disorder: Yellow skin and eyes, fever, generally unwell, muscle pain, rash, itching, abdominal pain, nausea, vomiting, loss of appetite, dark coloured urine		✓	
	Kidney Disorder: Severely decreased urine output		✓	

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

		Talk with your doctor or pharmacist		
	Low Level of Red Blood Cells: Pale skin, tiredness, breathlessness, dark urine		✓	
	Low Level of Blood Platelets: Spontaneous bleeding or bruising		✓	
	Low Blood Pressure: Dizziness on standing up,light-headedness, fainting			✓
	Myalgia: Joint Pain, muscle Pain	✓		
	Hypoglycemia: Low blood sugars in diabetic patients	✓		
Very rare	**Infection caused by decrease in white blood cells** (sore throat, fever)		✓	
	Impaired vision: Blurred vision, temporary loss of vision, seeing in a distorted manner, diminished vision			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
		Talk with your doctor or pharmacist		
Unknown	**Stroke:** numbness, tingling, weakness on one side of your body, vision changes, trouble speaking, walking or with balance, confusion, and severe headache			✓
	Depression: Sad mood, nervousness, sleep problems, tiredness	✓		
	Respiratory Problems: Shortness of breath, asthma, bronchitis		✓	

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

HOW TO STORE IT

- Store between 15°C and 30°C. Protect from moisture.
- Keep out of the reach and sight of children.
- Do not use after the expiry date shown on the box.
- Store in the original package.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.novartis.ca

or by contacting the sponsor,
Novartis Pharmaceuticals Canada Inc., at:
1-800-363-8883

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.
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Last revised: July 12, 2011
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