PRODUCT MONOGRAPH

PrLOTENSIN®

(benazepril hydrochloride)

5 mg and 20 mg tablets

Angiotensin Converting Enzyme Inhibitor

Novartis Pharmaceuticals Canada Inc.
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Date of Preparation:
June 7, 1993

Date of Revision:
March 23, 2015

Submission Control No: 180867

Table of Contents

[Pr]LOTENSIN®

(benazepril hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	5 mg and 20 mg tablets	Cellulose compounds, colloidal silicon dioxide, maize starch, crospovidone, hydrogenated castor oil, iron oxide, lactose, polyethylene glycol, talc and titanium dioxide. *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.*

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 AND PRECAUTIONS**).

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.

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 LOTENSIN in children have not been established, therefore its use in this age group is not recommended.

CONTRAINDICATIONS

LOTENSIN (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**).
- Patients with rare hereditary problems of galactose intolerance, e.g. galactosemia, the Lapp Lactase deficiency or glucose-galactose malabsorption because lactose is a non-medicinal ingredient in LOTENSIN.

Concomitant use of angiotensin-converting-enzyme inhibitors (ACEIs) - including LOTENSIN 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^2) 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, LOTENSIN 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 LOTENSIN, 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^2). Therefore, the use of LOTENSIN in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ACEIs, including LOTENSIN, 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 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.

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 LOTENSIN 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 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.

Immune

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).

Patients receiving co-administration of ACE inhibitors and mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema (see **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 LOTENSIN) 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

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.

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 LOTENSIN or of ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60ml/min/1.73m^2) (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 LOTENSIN (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, 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.

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 LOTENSIN 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 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 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 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:

Table 1 - Reported adverse events according to body systems

	LOTENSIN 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:

Less Common Clinical Trial Adverse Drug Reactions (<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 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 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 AND PRECAUTIONS)**.

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 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, agranulacytosis, 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 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 PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Proper name	Ref	Effect	Clinical comment
Agents Causing Renin Release	CT	The antihypertensive effect of LOTENSIN 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 LOTENSIN with agents causing renin release cannot be avoided".
Agents Increasing Serum Potassium	CT, C	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. Salt substitutes which contain potassium should also be used with caution.	Frequent Monitoring of serum potassium level.
Agents Affecting Sympathetic Activity	CT	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.	Close monitoring of blood pressure and dose adjustment may be required if coadministration of LOTENSIN with agents affecting sympathetic activity cannot be avoided.
Dual blockade of the Renin-Angiotensin-System (RAS) with ACEIs, ARBs or aliskiren-containing drugs	CT	There is evidence that co-administration of angiotensin-converting-enzyme inhibitors (ACEIs), including LOTENSIN, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal	The use of LOTENSIN in combination with aliskiren-containing drugs is contraindicated in these patients. Co-administration of ACEIs, including LOTENSIN, 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
		failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR<60ml/min/1.73m^2).	
Non steroidal anti-inflammatory drugs (NSAIDs)	CT, C	It has been shown that the hypotensive effect of ACE inhibitors may be reduced when administered concomitantly with indomethacin and other non-steroidal anti-inflammatory drugs. In a controlled clinical trial, indomethacin did not interfere with the antihypertensive effect of 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.	Monitoring of renal function and potassium level is recommended.

Proper name	Ref	Effect	Clinical comment
Oral Anticoagulants	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.	
Lithium	C	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.
Drugs causing angioedema	CT, C	The risk of angioedema may be increased in patients receiving co-administration of ACE inhibitors and drugs such as dipeptidyl peptidase-IV inhibitors or mTOR inhibitors (e.g. temsirolimus, sirolimus, and everolimus) (see **WARNINGS AND PRECAUTIONS Angioedema**).	Close monitoring may be required if concomitant administration cannot be avoided.
Other agents with antihypertensive properties	CT	LOTENSIN may increase the hypotensive effect of other antihypertensive agents.	Dosages must be adjusted accordingly.

Proper name	Ref	Effect	Clinical comment
Hydrochlorothiazide, Chlorthalidone and Furosemide	CT	The bioavailability of LOTENSIN was not altered when single doses were administered concomitantly with the diuretics hydrochlorothiazide, chlorthalidone or furosemide.	
Digoxin	CT	In a single dose interaction study of LOTENSIN with multiple doses of digoxin, no important changes[1] in pharmacokinetic parameters were observed.	
Amlodipine/Nifedipine	CT	LOTENSIN has been used concomitantly with the calcium channel blockers amlodipine and nifedipine, without evidence of clinically important adverse interactions.	
Insulin/Oral anti-diabetics	C	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. In case of persistent and/or severe hypoglycemia, dose adjustment or discontinuation of LOTENSIN should be considered.
Erythropoietin	T	Patient responsiveness to erythropoietin may decrease when use concomitantly with ACE inhibitors (including benazepril).	

Proper name	Ref	Effect	Clinical comment
Gold	T	Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.	Close monitoring of blood pressure may be required when coadministration with LOTENSIN cannot be avoided.
Probenecid	CT	Probenecid pretreatment may enhance the pharmacodynamic response of ACE inhibitors.	Dose adjustment may be necessary.
Other	CT	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.	

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

[1]The mean Cmax 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 Cmax 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 Cmax and AUC of Benazeprilat and Digoxin were observed when they were administered together.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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.

Recommended Dose and Dosage Adjustment

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.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

LOTENSIN (benazepril HCl) 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 LOTENSIN alone. Essentially no change in mean serum potassium was seen in patients treated with LOTENSIN 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 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 in all races studied, although it was somewhat less effective in blacks than in nonblacks.

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 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 2-4 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.

Pharmacokinetics

Absorption: 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.

Distribution: 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).

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 10-11 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

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

SPECIAL HANDLING INSTRUCTIONS

Not applicable

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability

LOTENSIN 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.

LOTENSIN 20 mg Tablets

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

Available in blister packages of 28 tablets.

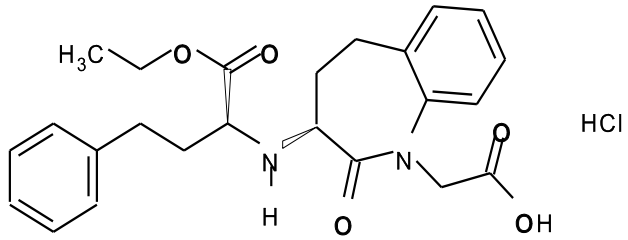
Composition

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

PART II: SCIENTIFIC INFORMATION

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.

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 ^{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

Table 3 - 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 effects in the female beagle. Emesis and anorexia were noted in beagles given oral doses ≥ 250 mg/kg and ≥ 500 mg/kg respectively. One dog was found dead on the fifth day post-dose after daily signs of emesis, anorexia, nasal discharge and reduced activity.

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 ♂ ≥ 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 ≥ 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 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.

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®
benazepril hydrochloride tablets

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

ABOUT THIS MEDICATION

What the medication is used for:
LOTENSIN lowers high blood pressure.

What it does:
LOTENSIN 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 LOTENSIN regularly even if you feel fine.

When it should not be used:
Do not take LOTENSIN if you:
- Are allergic to benazepril hydrochloride 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 LOTENSIN during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. LOTENSIN 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.
- If you have severe lactose intolerance or one of the following rare hereditary diseases:
  - Galactose intolerance
  - Lapp lactase deficiency
  - Glucose-galactose malabsorption

  Because lactose (milk sugar) is a non-medicinal ingredient in LOTENSIN.

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:
Tablets 5 mg and 20 mg.

WARNINGS AND PRECAUTIONS

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

BEFORE you use LOTENSIN 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.
- 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.
- 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 LOTENSIN 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 LOTENSIN 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 LOTENSIN.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to LOTENSIN. 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 LOTENSIN:
- 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 LOTENSIN exactly as prescribed. It is recommended to take your dose at about the same time every day.

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

The dose of LOTENSIN 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 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.

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 LOTENSIN 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.

LOTENSIN 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	

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	
Common	**Increased levels of potassium in the blood:** irregular heartbeat, muscle weakness and generally feeling unwell		✓	
	Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		✓	
Uncommon	**Electrolyte Imbalance:** weakness, drowsiness, muscle pain or cramps, irregular heartbeat		✓	
	Allergic Reactions, (Angioedema): Rash, hives, swelling of the face, eyes, lips or tongue, throat, arms or legs, or trouble swallowing or breathing			✓

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**	
	Low Blood Pressure: Dizziness, light-headedness, fainting. May occur when you go from lying or sitting to standing up	✓		
	Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓	
	Liver Disorder: Yellowing of the skin or eyes, abdominal pain, nausea, vomiting, loss of appetite, dark urine.		✓	

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**	
	Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
	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, trouble breathing, wheezing		✓	

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	
	Heart Attack: Sudden crushing chest pain, fast or irregular heartbeat, shortness of breath			✓
	Stevens-Johnson Syndrome: Rash, red skin, blistering of the lips, eyes or mouth, skin peeling, fever			✓
	Anemia: fatigue, loss of energy, weakness, shortness of breath		✓	
	Decreased Platelets: bruising, spontaneous bleeding, fatigue and weakness		✓	

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	
	Hypoglycemia: (low blood sugars in diabetic patients): Nervousness, sweating, trembling, weakness, palpitations	✓		
	Vision problems: 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 LOTENSIN, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

- Store between 15°C and 30°C. Protect from moisture and heat.
- **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 0701E
    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: March 23, 2015

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