PRODUCT MONOGRAPH

[Pr]MINT-LISINOPRIL

lisinopril tablets

5 mg, 10 mg and 20 mg of lisinopril as lisinopril dihydrate

USP

Angiotensin Converting Enzyme Inhibitor

Manufactured for:
Mint Pharmaceuticals Canada Inc.,
1 First Canadian Place, Suite 5600
100 King Street West
Toronto, Ontario
M5X 1E2

Date of Preparation:
September 29, 2008

Submission Control No: 124991

Table of Contents

PrMINT-LISINOPRIL

lisinopril tablets

5 mg, 10 mg and 20 mg of lisinopril as lisinopril dihydrate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablets, 5 mg, 10 mg and 20 mg	none *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Hypertension

MINT-LISINOPRIL (lisinopril) is indicated in the treatment of essential hypertension and in renovascular hypertension. It may be used alone or concomitantly with thiazide diuretics. A great majority of patients (>80%) with severe hypertension required combination therapy. Lisinopril has been used concomitantly with beta-blockers and calcium antagonists, but the data on such use are limited.

MINT-LISINOPRIL should normally be used in those patients in whom treatment with diuretic or beta blocker was found ineffective or has been associated with unacceptable adverse effects. MINT-LISINOPRIL 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.

Heart Failure

MINT-LISINOPRIL is indicated in the management of symptomatic congestive heart failure as adjunctive treatment with diuretics, and where appropriate, digitalis. Treatment with MINT-LISINOPRIL should be initiated under close medical supervision, usually in a hospital.

High doses of MINT-LISINOPRIL reduce the risk of the combined outcomes of mortality and hospitalization (see ACTION AND CLINICAL PHARMACOLOGY, and DOSAGE AND ADMINISTRATION).

Treatment Following Acute Myocardial Infarction

MINT-LISINOPRIL is indicated in the treatment of hemodynamically stable patients as early as within 24 hours following acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, ASA and beta-blocker(s).

Therapy with MINT-LISINOPRIL should be reassessed after 6 weeks. If there is no evidence of symptomatic or asymptomatic left ventricular dysfunction, treatment with MINT-LISINOPRIL can be stopped.

MINT-LISINOPRIL should not be used if systolic blood pressure is less than 100 mmHg, if clinically relevant renal failure is present, or if there is a history of bilateral stenosis of the renal arteries (see WARNING AND PRECAUTIONS – Cardiovascular - *Hypotension Following Acute Myocardial Infarction*, – Renal Impairment)

General

In using MINT-LISINOPRIL, attention should be given to the risk of angioedema (see WARNINGS AND PRECAUTIONS – General - *Angioedema*).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients who have a known allergy to angiotensin-converting enzyme inhibitors.
- Patients who have a history of angioneurotic edema relating to previous treatment with an angiotensin-converting enzyme inhibitor.
- Patients who have hereditary or idiopathic angioneurotic edema.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, MINT-LISINOPRIL should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS – Special Populations – Pregnant Women and PART III: CONSUMER INFORMATION.

General

Angioedema

Angioedema has been reported in patients treated with Lisinopril and may occur at any time during therapy. Angioedema associated with laryngeal or tongue oedema and/or shock may be fatal. If angioedema occurs, MINT-LISINOPRIL should be promptly discontinued and the patient should be treated, and observed until the swelling subsides. Where swelling is confined only to the tongue, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, and especially in cases where there has been a history of airway surgery, emergency therapy should be administered promptly when indicated. This includes giving subcutaneous adrenaline (0.5 mL 1:1000), and/or maintaining a patent airway. The patient should be under close medical supervision until complete and sustained symptom resolution has occurred.

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

Cardiovascular

Hypotension

Symptomatic hypotension has occurred after administration of Lisinopril, 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, vomiting, or possibly in patients with renin-dependant renovascular hypertension (see DOSAGE AND ADMINISTRATION). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because blood pressure could potentially fall, patients at risk for hypotension should start therapy under very close medical supervision, usually in a hospital. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of lisinopril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS).

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response may not be a contraindication to further doses. These can usually be given to hypertensive patients without difficulty once the blood pressure has increased after volume expansion. However, lower MINT-LISINOPRIL doses and/or reduced concomitant diuretic therapy should be considered.

If hypotension occurs during treatment following acute myocardial infarction, consideration should be given to MINT-LISINOPRIL discontinuation (see ADVERSE REACTIONS, and DOSAGE AND ADMINSTRATION – Treatment Following Acute Myocardial Infarction).

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with MINT-LISINOPRIL. If hypotension occurs, a reduction of dose or discontinuation of therapy should be considered.

Hypotension Following Acute Myocardial Infarction

Lisinopril treatment following acute myocardial infarction must not be initiated in patients at risk of further serious hemodynamic deterioration after vasodilator treatment.

These include patients with systolic blood pressure of 100 mmHg or lower or those in cardiogenic shock.

During the first 3 days following the infarction, dosage reduction should occur if systolic blood pressure is between 100 and 120 mmHg (see DOSAGE AND ADMINISTRATION – Treatment Following Acute Myocardial Infarction).

Patients with myocardial infarction in the GISSI-3 study treated with lisinopril, had a higher (9.0% vs 3.7%) incidence of persistent hypotension (systolic blood pressure less than 90 mmHg for more than 1 hour) than placebo.

Valvular Stenosis, Hypertrophic Cardiomyopathy

There is concern on theoretical grounds that patients with aortic stenosis or hypertrophic cardiomyopathy might be at particular risk of decreased coronary perfusion when treated with vasodilators.

MINT-LISINOPRIL should be given with caution to these patients.

Hyperkalemia

In clinical trials with daily doses of 2.5 to 20 mg, hyperkalemia (serum potassium >5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients.

As shown in the ATLAS trial (see ACTION AND CLINICAL PHARMACOLOGY), high dose (up to 35 mg) versus low dose (up to 5 mg) treatment may predispose CHF patients to hyperkalaemia (6.4% versus 3.5%). This event was manageable and rarely led to treatment withdrawal. Therapy discontinuation rates due to hyperkalaemia for high versus low dose were 0.4% versus 0.1 %, respectively. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics,

potassium supplements and/or potassium-containing salt substitutes. (See DRUG INTERACTIONS).

Hematologic

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression have been caused by angiotensin converting enzyme inhibitors. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and renal disease.

Hepatic/Biliary/Pancreatic

Patients with Impaired Liver Function

Hepatitis – either hepatocellular or cholestatic-, jaundice, marked elevations of liver enzymes and/or serum bilirubin have occurred during therapy with lisinopril in patients with or without pre-existing liver abnormalities (see ADVERSE REACTIONS). Very rarely it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving MINT-LISINOPRIL who develop jaundice or marked elevation of hepatic enzymes should discontinue MINT-LISINOPRIL and receive appropriate medical follow-up. Should the patient receiving MINT-LISINOPRIL experience any unexplained symptoms (see CONSUMER INFORMATION), particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigation be carried out. Discontinuation of MINT-LISINOPRIL should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. MINT-LISINOPRIL 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.

Diabetic Patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with MINT-LISINOPRIL (see DRUG INTERACTIONS - Drug-Drug Interactions).

Immune

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes [e.g.: polyacrylonitrile (PAN) and during low-density lipoproteins (LDL) apheresis with dextran

sulphate] and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

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 Consideration

Surgery/Anesthesia

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, lisinopril blocks angiotensin II formation, secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Renal 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.

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/L and/or proteinuria exceeding 500 mg/24 h. If renal dysfunction develops during treatment with MINT-LISINOPRIL (serum creatinine concentration exceeding 265 micromol/L or a doubling from the pre-treatment value), then the physician should consider withdrawal of MINT-LISINOPRIL.

Use of MINT-LISINOPRIL (lisinopril) should include appropriate assessment of renal function.

Respiratory

Cough

A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of lisinopril, has been reported.

Such a possibility should be considered as part of the differential diagnosis of the cough.

Special Populations

Pregnant Women: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, MINT-LISINOPRIL 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.

Lisinopril has been removed from the neonatal circulation by peritoneal dialysis.

Animal Data

Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1000 mg/kg, this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.

Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man.

Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the

lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88% to 100% fetal death.

By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses.

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: Safety and effectiveness in children have not been established.

Geriatrics (> 65 years of age)

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril (see DOSAGE AND ADMINISTRATION – Dosage in the Elderly)

Race

Angiotensin converting inhibitors cause a higher rate of angioedema in black patients than in non black patients.

The antihypertensive effect of angiotensin converting enzyme inhibitors is generally lower in black patients (usually a low-renin hypertensive population) than in non-black patients.

Occupation Hazards
Ability to drive and use machines: dizziness or tiredness may occur during treatment with MINT-LISINOPRIL.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
In controlled clinical trials involving 3269 patients, 2633 patients with hypertension and 636 patients with congestive heart failure, excluding the ATLAS CHF study patients (see ACTION and CLINICAL PHARMACOLOGY), the most frequent clinical adverse reactions were: dizziness (4.4%), headache (5.6%), asthenia/fatigue (2.7%), diarrhea (1.8%) and cough (3.0%), all of which were more frequent than in placebo-treated patients. Discontinuation of therapy was required in 5.9% of patients.

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*.

For adverse reactions which occurred in hypertensive patients and patients with congestive heart failure treated with lisinopril in controlled clinical trials, comparative incidence data are listed in Table 1 below.

Adverse Events in Controlled Clinical Trials

Incidence of adverse reactions occurring in patients treated with lisinopril in controlled clinical trials.

Table 1		Hypertension n = 2633 (%)	Congestive Heart Failure n = 636 (%)
Cardiovascular	hypotension	0.8	5.2
	orthostatic effects	0.9	1.3
	chest pain	1.1	7.4
	angina	0.3	3.8
	edema	0.6	2.5
	palpitation	0.8	1.9
	rhythm disturbances	0.5	0.6
Gastrointestinal	diarrhea	1.8	6.1
	nausea	1.9	4.9
	vomiting	1.1	2.4
	dyspepsia	0.5	1.9
	anorexia	0.4	1.4
	constipation	0.2	0.8
	flatulence	0.3	0.5
Nervous System	dizziness	4.4	14.2
	headache	5.6	4.6
	paresthesia	0.5	2.8
	depression	0.7	1.1
	somnolence	0.8	0.6
	insomnia	0.3	2.4
	vertigo	0.2	0.2
Respiratory	cough	3.0	6.4
	dyspnea	0.4	7.4
	orthopnea	0.1	0.9
Dermatologic	rash	1.0	5.0
	pruritus	0.5	1.4
Musculoskeletal	muscle cramps	0.5	2.2
	back pain	0.5	1.7
	leg pain	0.1	1.3
	shoulder pain	0.2	0.8
Other	asthenia/fatigue	2.7	7.1

Table 1		Hypertension n = 2633 (%)	Congestive Heart Failure n = 636 (%)
	blurred vision	0.3	1.1
	fever	0.3	1.1
	flushing	0.3	0.3
	gout	0.2	1.7
	decreased libido	0.2	0.2
	malaise	0.3	1.1

Angioedema

Angioedema has been reported in patients receiving lisinopril (0.1%). In very rare cases, intestinal angioedema has been reported. (See WARNINGS AND PRECAUTIONS – General - *Angioedema*).

Hypotension

In hypertensive patients, hypotension occurred in 0.8% and syncope occurred in 0.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.3% of hypertensive patients (see WARNINGS AND PRECAUTIONS – Cardiovascular - *Hypotension*).

In patients with congestive heart failure, hypotension occurred in 5.2% and syncope occurred in 1.7% of patients. Hypotension and dizziness were causes for discontinuation of therapy in 1.7% of these patients.

As shown in the ATLAS trial (see ACTION AND CLINICAL PHARMACOLOGY), high dose (up to 35 mg) versus low dose (up to 5 mg) treatment may predispose patients to hypotension-related symptoms such as: dizziness (18.9% versus 12.1%), syncope (7.0% versus 5.1%), and hypotension (10.8% versus 6.7%). These events were manageable and rarely led to treatment withdrawal. Therapy discontinuation rates for high versus low dose were: dizziness 0.3 and 0%, hypotension 0.8% and 0.6%, and for syncope 0.3% and 0.3%, respectively.

Treatment Following Acute Myocardial Infarction

In a controlled, open trial, involving 19,394 acute myocardial infarction patients (GISSI-3; see INDICATIONS AND CLINICAL USE - Treatment Following Acute Myocardial Infarction), comparing lisinopril alone, transdermal glycerol trinitrate, lisinopril and transdermal glycerol trinitrate, or control (no treatment), the most frequent in-hospital adverse events were as follows in Table 2:

Table 2

Event	Control n = 4729	Lisinopril n = 4713	Lisinopril + GTN n = 4722	GTN Alone n = 4731
Persistent Hypertension	3.6	8.8	9.3	3.9
Shock	2.5	2.8	2.2	1.9
Renal Dysfunction	1.1	2.4	2.4	1.1
Stroke	0.6	0.6	0.9	0.8
Re-Infarction	2.2	2.2	2.2	1.9
Hemorrhagic Events	1.2	1.3	1.1	0.9
Post-Infarction Angina	13.2	13.9	12.3	11.8
Ventricular Fibrillation	3.1	2.5	2.4	2.2
Sustained Ventricular Tachycardia	2.5	2.1	1.8	2.3
Atrial Flutter or Fibrillation	6.4	6.3	5.3	5.7
Complete Atrioventricular Block	2.4	2.9	2.5	2.1
Asystole	1.2	1.2	1.3	1.2
Intraventricular Septal Rupture	0.3	0.4	0.2	0.2
Papillary Muscle Rupture	0.3	0.4	0.5	0.4
Late CHF (>4 days)	4.5	4.5	4.2	4.2

Abnormal Hematologic and Clinical Chemistry Findings

Serum Electrolytes

Hyperkalemia (see WARNINGS AND PRECAUTIONS - Hyperkalemia).

Creatinine, Blood Urea Nitrogen

Increases in blood urea nitrogen and serum creatinine, usually reversible upon discontinuation of therapy, were observed in 1.1 and 1.6% of patients respectively with essential hypertension treated with lisinopril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see WARNINGS AND PRECAUTIONS -

Renal Impairment). In patients with congestive heart failure on 2.5 to 20 mg lisinopril and concomitant diuretic therapy, reversible increases in blood urea nitrogen (14.5%) and serum creatinine (11.2%) were observed in approximately 12.0% of patients. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

As shown in the ATLAS trial (see ACTION AND CLINICAL PHARMACOLOGY), high dose (up to 35 mg) versus low dose (up to 5 mg) treatment may predispose patients to increased serum creatinine (9.9% versus 7.0%). This event was manageable and rarely led to treatment withdrawal. Therapy discontinuation rates due to increased serum creatinine for high versus low dose were 0.3% versus 0.4%, respectively.

Hematology

Decreases in hemoglobin and hematocrit (mean decreases of approximately 0.9 g% and 0.6 vol%, respectively) occurred frequently in patients treated with Lisinopril but were rarely of clinical importance in patients without some other cause of anemia. Rarely, hemolytic anemia has been reported.

Agranulocytosis and bone marrow depression, manifested as anemia, cytopenia or leucopenia, have been caused by angiotensin converting enzyme inhibitors, including lisinopril. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded (see WARNINGS AND PRECAUTIONS – Hematologic – *Neutropenia/Agranulocytosis*).

Hepatic

Elevations of liver enzymes and/or serum bilirubin have occurred (see WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic – *Patients with Impaired Liver Function*).

Discontinuations

Overall, 1.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.8%), serum creatinine (0.1%) and serum potassium (0.1%).

Post-Market Adverse Drug Reactions

The following undesirable effects have been observed and reported during treatment with lisinopril with the following frequencies: Very common (≥ 10%), common (≥ 1%, < 10%), uncommon (≥ 0.1%, < 1%), rare (≥ 0.01%, < 0.1%), very rare (< 0.01%) including isolated reports.

Blood and lymphatic system disorders

Very rare: bone marrow depression, anemia thrombocytopenia, leucopenia, agranulocytosis, hemolytic anemia (see WARNINGS AND PRECAUTIONS – Hematologic - *Neutropenia/Agranulocytosis*).

Metabolism and nutrition disorders

Uncommon: hyperkalemia (see WARNINGS AND PRECAUTIONS - Hyperkalemia).
Rare: hyponatremia.
Very rare: hypoglycaemia (see WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic – *Diabetic Patients*).

Nervous system and psychiatric disorders

Common: dizziness, headache.
Uncommon: mood alterations, paraesthesia**,** vertigo, taste disturbance, sleep disturbances.
Rare: mental confusions.

Cardiac and vascular disorders

Common: orthostatic effects (including hypotension) (see WARNINGS AND PRECAUTIONS – Cardiovascular - *Hypotension*).
Uncommon: myocardial infarction or cerebrovascular accident (both possibly secondary to excessive hypotension in high risk patients (see WARNINGS AND PRECAUTIONS – Cardiovascular – *Hypotension Following Acute Myocardial Infarction*), palpitations**,** tachycardia.

Respiratory, thoracic and mediastinal disorders:

Common: cough.
Uncommon: rhinitis.
Very rare: bronchospasm, sinusitis.

Gastrointestinal disorders

Common: diarrhoea, vomiting.
Uncommon: nausea, abdominal pain and indigestion.
Rare: dry mouth.
Very rare: pancreatitis, intestinal angioedema (See WARNINGS AND PRECAUTIONS – General - *Angioedema* and ADVERSE REACTIONS - Angioedema).

Hepato-biliary disorders

Very rare: hepatitis – either hepatocellular or cholestatic, jaundice, hepatic failure. Very rarely it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril who develop jaundice or marketed elevation of hepatic enzymes should discontinue

MINT-LISINOPRIL and receive appropriate medical follow-up (See WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic – *Patients with Impaired Liver Function*).

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritis.

Rare: hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis, and/or larynx (See WARNINGS AND PRECAUTIONS – General - *Angioedema*), urticaria, alopecia, psoriasis.

Very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Steven-Johnson Syndrome, erythema multiforme.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), oesinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders

Common: renal dysfunction.

Rare: uremia, acute renal failure.

Very rare: oliguria/anuria (see WARNINGS AND PRECAUTIONS – Renal Impairment).

Reproductive system and breast disorders

Uncommon: impotence.

General disorders and administration site conditions

Uncommon: fatigue, asthenia

Investigations

Uncommon: increases in blood urea, increases in serum creatinine (see WARNINGS AND PRECAUTIONS – Renal Impairment), increases in liver enzymes (see WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic – *Patients with Impaired Liver Function*).

Rare: decreases in hemoglobin, decreases in hematocrit, increases in serum bilirubin (see WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic – *Patients with Impaired Liver Function*).

DRUG INTERACTIONS

Drug-Drug Interactions

Hypotension - Patients on Diuretic Therapy

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may

occasionally experience an excessive reduction of blood pressure after initiation of therapy with lisinopril. The possibility of symptomatic hypotension with lisinopril can be minimized by discontinuing the diuretic prior to initiation of treatment with lisinopril and/or lowering the initial dose of lisinopril (See WARNINGS AND PRECAUTIONS – Cardiovascular - *Hypotension* and DOSAGE AND ADMINISTRATION).

Hypotension - Patients on Antihypertensive Therapy
When lisinopril is given to patients already treated with other antihypertensive agents, further falls in blood pressure may also occur.

Potassium Supplements, potassium-sparing agents or potassium-containing salt substitutes
Since lisinopril decreases aldosterone production, elevation of serum potassium may occur. Potassium sparing diuretics such as spironolactone, triamterene or amiloride, or potassium supplements should be given only for documented hypokalemia and with caution and with frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Potassium-containing salt substitutes should also be used with caution.

Agents Causing Renin Release
The antihypertensive effect of MINT-LISINOPRIL is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

Agents Affecting Sympathetic Activity
Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to lisinopril.

NSAIDS
In some patients with compromised renal function, lisinopril co-administration with non-steroidal anti-inflammatory drugs (NSAIDs) may produce further renal function deterioration.

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered MINT-LISINOPRIL.

Lithium Salts
As with other drugs which eliminate sodium, lithium elimination may be reduced. Therefore, the serum lithium levels should be monitored carefully if lithium salts are to be administered.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Drug-Food Interactions
Since absorption of MINT-LISINOPRIL tablets is not affected by food, the tablets may be administered before, during or after meals.

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

DOSAGE AND ADMINISTRATION

Essential Hypertension

In patients with essential hypertension, not on diuretic therapy, the usual recommended starting dose is 10 mg once a day. The usual dosage range is 10 to 40 mg per day, administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. 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, an increase in dose should be considered. The maximum dose used in long-term controlled clinical trials was 80 mg/day. If blood pressure is not controlled with MINT-LISINOPRIL alone, a low dose of diuretic may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of diuretic, it may be possible to reduce the dose of MINT-LISINOPRIL.

Diuretic Treated Patients

In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of MINT-LISINOPRIL. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with MINT-LISINOPRIL to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS – Cardiovascular - *Hypotension*). The dosage of MINT-LISINOPRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with MINT-LISINOPRIL alone, diuretic therapy may be resumed as described above.

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS AND PRECAUTIONS - Cardiovascular - *Hypotension* and DRUG INTERACTIONS – Drug-Drug Interactions – "Hypotension – Patients on Diuretic Therapy").

A lower starting dose is required in the presence of renal impairment, in patients in whom diuretic therapy cannot be discontinued, patients who are volume and/or salt-depleted for any reason, and in patients with renovascular hypertension.

Dosage Adjustment in Renal Impairment
Dosage in patients with renal impairment should be based on creatinine clearance as outlined in the table below:

Creatinine Clearance		Starting Dose mg/day
mL/s	mL/min	
0.50-1.17	31-70	5.0-10.0
0.17-0.50	10-30	2.5-5.0
<0.17 (including patients on dialysis)	<10 (including patients on dialysis)	2.5*

*Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.: polyacrylonitrile [PAN] and during low-density lipoproteins (LDL) apheresis with dextran sulphate) and treated concomitantly with an ACE inhibitor (see WARNINGS AND PRECAUTIONS – Immune – *Anaphylactoid Reactions During Membrane Exposure*).

Dosage in the Elderly
In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Renovascular Hypertension

Some patients with renovascular hypertension, especially those with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, may develop an exaggerated response to the first dose of MINT-LISINOPRIL. In these patients, treatment should be started at low doses (2.5 or 5 mg), under close medical supervision. Thereafter, the dosage may be adjusted according to the blood pressure response. Doses should be carefully titrated.

Congestive Heart Failure

MINT-LISINOPRIL is to be used in conjunction with diuretics, and where appropriate digitalis. Therapy must be initiated under close medical supervision, usually in a hospital. Blood pressure and renal function should be monitored, both before and during treatment with MINT-LISINOPRIL, because severe hypotension and, more rarely, consequent renal failure have been

reported (see WARNINGS AND PRECAUTIONS – Cardiovascular – *Hypotension*, - Renal Impairment).

Initiation of therapy requires consideration of recent diuretic therapy and the possibility of severe salt/volume depletion. If possible, the dose of diuretic should be reduced before beginning treatment.

The recommended initial dose is 2.5 mg per day. The MINT-LISINOPRIL dose should be increased:

- by increments of no greater than 10 mg,
- at intervals of no less than 2 weeks, up to a maximum of 35 mg once daily. Dose adjustment should be based on the individual patient's tolerance and clinical response.

Treatment Following Acute Myocardial Infarction

Treatment with MINT-LISINOPRIL may be started as early as within 24 hours following the onset of symptoms in hemodynamically stable patients. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, ASA and beta-blocker(s) (see INDICATIONS AND CLINICAL USE - Treatment Following Acute Myocardial Infarction).

The first dose of MINT-LISINOPRIL is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily thereafter.

Patients with a low systolic blood pressure (between 100 and 120 mmHg) when treatment is started or during the first 3 days after the infarct should be given a lower dose - 2.5 mg orally. Treatment with MINT-LISINOPRIL must not be initiated in patients who are at risk of serious hemodynamic deterioration (see WARNINGS AND PRECAUTIONS – Cardiovascular – *Hypotension Following Acute Myocardial Infarction*). After three days, if hypotension occurs (systolic blood pressure less than or equal to 100 mmHg), a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour), MINT-LISINOPRIL should be withdrawn.

Renal function should be assessed before and during therapy with MINT-LISINOPRIL (see WARNINGS AND PRECAUTIONS – Renal Impairment).

Dosing should normally continue for six weeks. At that time, patients with signs or symptoms of heart failure should continue with MINT-LISINOPRIL (see DOSAGE AND ADMINISTRATION - Congestive Heart Failure).

Administration

Since absorption of MINT-LISINOPRIL is not affected by food, the tablets may be administered before, during or after meals.

MINT-LISINOPRIL should be administered in a single daily dose.

MINT-LISINOPRIL should be taken at the same time each day.

Dosage must be individualized and should be adjusted according to blood pressure response.

OVERDOSAGE

Overdose symptoms include severe hypotension, electrolyte disturbances, and renal failure. Overdosed patients should be kept under very close observation. Therapeutic measures depend on the nature and severity of symptoms. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, place the patient in the shock position and infuse intravenous normal saline immediately. Vasopressors including angiotensin II may be considered if fluid replacement is inadequate or contraindicated. Circulating lisinopril may be removed by hemodialysis. Avoid high-flux polyacrylonitrile dialysis membranes (see WARNINGS AND PRECAUTIONS – Immune - *Anaphylactoid Reactions During Membrane Exposure*). Serum electrolytes and creatinine should be monitored frequently.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lisinopril is an ACE inhibitor, which is used in the treatment of hypertension, congestive heart failure and following myocardial infarction in hemodynamically stable patients.

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance, angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release) and decreased aldosterone secretion. Although the latter decrease is small, it results in a small increase in serum K^+. In patients treated with Lisinopril and a thiazide diuretic there was essentially no change in serum potassium (see WARNINGS AND PRECAUTIONS).

ACE is identical to kininase II. Thus, Lisinopril may also block the degradation of bradykinin, a potent vasodilator peptide. However, the role that this plays in the therapeutic effects of Lisinopril is unknown.

While the mechanism through which Lisinopril lowers blood pressure is believed to be primarily the suppression of the renin-angiotensin-aldosterone system, Lisinopril also lowers blood pressure in patients with low-renin hypertension.

Administration of lisinopril to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure. In most patients studied, after oral administration of an individual dose of lisinopril, the onset of antihypertensive activity is seen at one hour with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing. On occasion, achievement of optimal blood pressure reduction may require 2 to 4 weeks of therapy.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of lisinopril, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of Lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

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

Administration of Lisinopril to patients with congestive heart failure reduces afterload and preload of the heart, resulting in an increase in cardiac output, without reflex tachycardia. Exercise tolerance is improved.

In the Assessment of Treatment with Lisinopril and Survival Study (ATLAS) higher doses of lisinopril up to 35 mg once daily reduced the risk of the combined outcome of mortality and hospitalization in patients with chronic congestive heart failure. The ATLAS study was an international, multicenter, double-blind, parallel group clinical trial which evaluated the effects of low doses, 2.5 mg-5.0 mg, versus high doses, 32.5 mg-35.0 mg lisinopril on mortality and morbidity in patients with chronic congestive heart failure. A total of 1596 patients were randomized into the low dose and 1568 into the high dose groups. Patients entered into the ATLAS study were NYHA Class II, III, or IV, were treated with diuretics for at least 60 days prior to entry into the study, and had a left ventricular ejection fraction (LVEF) ≤ 30%. Class II patients were eligible only if they were hospitalized or received emergency room treatment in the previous six months. Prior treatment with ACE inhibitors and digoxin was permitted, and patients were permitted routine therapies, other than ACE inhibitors, for the duration of the

study. The median follow-up period was 46 months. The protocol excluded patients with recent cardiac surgery, unstable coronary artery disease, unstable ventricular arrhythmias, unstable CHF, or a non-CHF disorder that may have limited survival during the course of the trial. Overall, 77% of patients were NYHA class III; 89% had previous ACE inhibitor treatment. For the principal secondary endpoint, all-cause mortality and all-cause hospitalization, high dose lisinopril was associated with an 11.6% (p=0.002) risk reduction over low dose (2.5 and 5 mg). High dose lisinopril was also associated with an 8.4% risk reduction in all-cause mortality and cardiovascular hospitalizations (p =0.036). The total number of hospitalizations per patient for heart failure was reduced by 23.2% (p=0.002).

In a double-blind, randomized, placebo controlled, parallel group study carried out in normotensive patients with insulin-dependent diabetes mellitus of relatively short duration (mean 14-15 years), the effect on the development and progression of diabetic retinopathy was examined in a subgroup of 354 patients with evaluable retinal photographs treated with a daily dose of 10 to 20 mg lisinopril or placebo for up to 24 months. Preliminary data obtained in 103 patients with mild to moderate retinopathy and 72 patients with no retinopathy at baseline indicate that treatment with lisinopril resulted in a significant risk reduction in the progression of retinopathy compared to placebo. There was, however, no significant effect on the incidence of either the appearance of new cases or the regression of existing cases of retinopathy over a two-year observation period.

Pharmacokinetics

Absorption: After oral administration of lisinopril, peak serum concentrations of lisinopril occur within approximately 7 hours, although patients with recent myocardial infarction have demonstrated an increase in time to peak serum concentration to about 8 to 10 hours. Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not bind serum proteins other than ACE.

Lisinopril absorption is not influenced by the presence of food in the gastrointestinal tract.

Distribution: Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Metabolism: Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine. Based on urinary recovery, the extent of absorption of lisinopril is approximately 25%, with large inter-subject variability (6-60%) at all doses tested (5-80 mg).

Following multiple doses of lisinopril, the effective half-life of accumulation is 12 hours.

Excretion: Lisinopril can be removed by dialysis.

Special Populations and Conditions

Geriatrics: In a study in elderly healthy subjects (65 years and above), a single dose of lisinopril 20 mg produced higher serum concentrations and higher values for the area under the plasma curve than those seen in young healthy adults given a similar dose. In another study, single daily doses of lisinopril 5 mg were given for 7 consecutive days to young and elderly healthy volunteers and to elderly patients with congestive heart failure. Maximum serum concentrations of lisinopril on Day 7 were higher in the elderly volunteers than in the young, and still higher in the elderly patients with congestive heart failure. Renal clearance of lisinopril was decreased in the elderly, particularly in the presence of congestive heart failure.

Renal Insufficiency: Impaired renal function decreases elimination of lisinopril. This decrease becomes clinically important when the glomerular filtration rate is below 30 mL/min (see WARNINGS AND PRECAUTIONS – Renal Impairment, and DOSAGE AND ADMINISTRATION).

Genetic Polymorphism: No data is available.

STORAGE AND STABILITY

Store at room temperature (15 -30ºC). Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MINT-LISINOPRIL (lisinopril) 5 mg Tablets
Each light pink colored, round flat face, beveled edge bisect tablets debossed with 'RX' above the bisect and '532' below the bisect on one side and plain on the other side, contains: lisinopril 5 mg as lisinopril dihydrate. Nonmedicinal ingredients: corn starch, dibasic calcium phosphate (anhydrous), magnesium stearate, mannitol, pregelatinized starch and red iron oxide.

MINT- LISINOPRIL (lisinopril) 10 mg Tablets
Each light pink colored, round flat face, beveled edge tablets debossed with 'RX533' on one side and plain on the other side, contains: lisinopril 10 mg as lisinopril dihydrate. Nonmedicinal ingredients: corn starch, dibasic calcium phosphate (anhydrous), magnesium stearate, mannitol, pregelatinized starch and red iron oxide.

MINT- LISINOPRIL (lisinopril) 20 mg Tablets
Each light rust colored, round flat face, beveled edge tablets debossed with 'RX534' on one side and plain on the other side, contains: lisinopril 20 mg as lisinopril dihydrate. Nonmedicinal ingredients: corn starch, dibasic calcium phosphate (anhydrous), magnesium stearate, mannitol, pregelatinized starch and red iron oxide.

MINT- LISINOPRIL (lisinopril) 5 mg, 10 mg and 20 mg tablets are available in Bottles of 100's and 500's.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

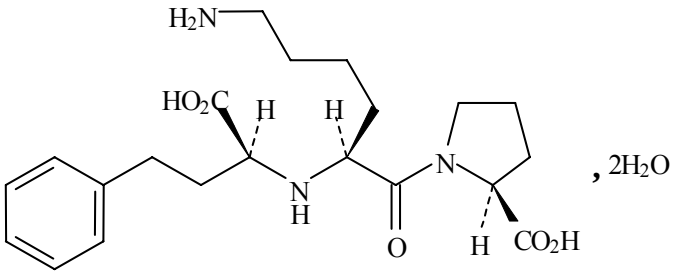
Drug Substance

Proper name: lisinopril

Chemical name: S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate

Molecular formula (molecular mass): $C_{21}H_{31}N_30_5.2H_20$ (441.53)

Structural formula:



Physicochemical properties: Lisinopril is a white to off-white, crystalline powder. It is soluble in water and sparingly soluble in methanol and practically insoluble in ethanol.

CLINICAL TRIALS

A blinded, comparative, randomized, 2-way crossover study was performed under fasting conditions in 27 healthy adult male volunteers. The study compared the rate and extent of absorption of a single oral dose (1 x 20 mg) of MINT-Lisiniopril Tablets or Zestril® (lisinopril) Tablets. A summary of the pharmacokinetic parameters is given in the table below.

Lisinopril
(1 x 20 mg Tablets)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	MINT-LISINOPRIL 20 mg Tablet	Zestril® 20 mg Tablets†	% Ratio of Geometric Means**	90% Confidence Interval
AUC_{0-72} (ng•h/mL)	1101.33 1153.5 (30.0)	1068.42 1121.8 (31.6)	103.1	94.1-112.9
$AUC_{I\ inf}$ (ng•h/mL)	1136.05 1188.2 (29.4)	1123.40 1177.1 (30.4)	101.1	92.6-110.4
C_{MAX} (ng/mL)	84.0893 88.707 (31.9)	82.1249 86.911 (33.7)	102.4	92.9-112.8
T_{MAX}§ (h)	6.667 (8.6)	6.593 (17.4)		
$T_{½}$§ (h)	19.627 (36.3)	19.884 (36.2)		

† Zestril® 20 mg Tablets AstraZeneca Canada Inc. (purchased in Canada)
§ Expressed as arithmetic mean (CV%)
** Based on least square estimate

DETAILED PHARMACOLOGY

Mechanism of Action

Study	Species/Strain	Number of Animals/ Group	Route	Dose	Results
in vitro ACE inhibitory	hog plasma		*in vitro*		ICSO= ± 0.5 nM
augmentation of contractile reesponse to bradykinin	guinea pig ileum	*7* segments	*in vitro*		AC_{50} = 1.6nM
in vivo ACE inhibition in the rat**	male Sprague/Dawley	8	i.v.		ID_{50} = 2.3 (1.7-3.1) pg/kg
duration of ACE inhibitory activity of lisinopril in rats**	male Sprague/Dawley	4	i.v.	3 & 10 pg/kg	Duration approx. 110 min.
in vivo ACE inhibitory activity of lisinopril in conscious rats**	Sprague/Dawley	3 - 5	p.o.	0.03-3.0 mg/kg (single dose)	Duration of at least 360 mins.
in vivo ACE inhibition in anesthetized dogs**	mongrel	6	i.v.	1-30 pg/kg	ID_{50} = 6.5 pg/kg
in vivo ACE inhibitory activity of lisinopril in conscious dogs**	mongrel	3	p.o.	0.05-1.0 mg/kg (single dose)	Duration of action of between 6-24 hrs.

* Inhibition of enzymatic activity of hog plasma ACE using ^{14}C labeled substrate.
** Blockage of functional (pressor) response to Al challenge.

Effects on Blood Pressure

Study	Species/Strain	Number of Animals/Group	Route	Dose	Results
antihypertensive activity in renal hypertensive dogs (single doses)	Mongrel	3	p.o.	0.3 mg/kg with and without hydro-chlorothiazide	After 2 hours: Lisinopril alone: 5% reduction in mean systolic pressure vs pretreatment. Lisinopril + HCTZ = 11% reduction in mean systolic pressure vs pretreatment.

Study	Species/Strain	Number of Animals/Group	Route	Dose	Results
antihypertensive activity in rats on a sodium-deficient diet	Male Sprague/ Dawley	5	p.o.	0.03-3.0 mg/kg daily for 4 days	After 2 hours: 11% reduction in mean systolic pressure vs pretreatment at 1 mg/kg. 22% reduction in mean systolic pressure vs pretreatment at 3 mg/kg. Consistent response over 4 days.
antihypertensive activity in 2 kidney Grollman hypertensive rats (single doses)	Male Sprague/ Dawley	6 - 7	p.o.	1 & 3 mg/kg	At 2 hours: approx. 6% reduction in mean systolic pressure vs pretreatment with the antihypertensive effect lasting up to 24 hours.
antihypertensive activity in spontaneously hypertensive rats with and without hydrochlorothiazide	SH rats	3 - 6	p.o.	1.25 mg/kg HCTZ = 50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3-5 days. 2 hours after drug administration, lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ the average mean arterial pressure was reduced from 202 to 132 mmHg.
antihypertensive activity in spontaneously hypertensive rats (single doses)	SH rats	3 - 9	p.o. & i.v.	0.1-20 mg/kg	Slight fall in blood pressure at 0.312-5 mg/kg P.O. Pronounced fall at 20 mg/kg P.O. and 0.1 mg/kg i.v. with statistically significant reductions being observed for the majority of time points between 1/2-18 hours.

TOXICOLOGY

Acute Toxicity of Lisinopril
LD_{50} Values

Route	Species	Sex	LD_{50} (g/kg)
Oral	Mouse	male	>20
	Mouse	female	>20
	Rat	male	>20
	Rat	female	>20
	Dog	male	>6
	Dog	female	>6
Intravenous	Mouse	male	>10
	Mouse	female	>10
Intraperitoneal	rat	male	>10
	rat	female	>10

Signs of toxicity: Following oral administration to mice decreased activity and one male death (1/10) occurred. No signs of toxicology occurred in rats after oral administration. Dogs given 6 g/kg had transient diarrhea and increases in serum urea nitrogen. Intravenous administration to mice produced bradypnea, ataxia, clonic convulsions, exophthalmia, and tremors. After intraperitoneal administration in rats, ataxia and one female death (1/10) occurred. No signs of toxicology or death occurred in the males.

Subacute/Chronic Toxicology

Species	Duration	No. Of Animals/Group	Route	Dose mg/kg/day	Effects
Rat	2-week	10 F + 10 M	Oral	3,10,30	At all doses, decreases of 2 to 16% in weight gain and 12 to 14% in heart weights were observed in female rats.
Rat	3-month with 1-month Interim	25 F + 25 M	Oral	3,10,30	At all doses, increased serum urea nitrogen values (up to approximately 2-fold) and decreased heart weights (7 to10%) were observed in female rats. At 10 and 30 mg respectively weight gain decreased 11 to 14% in males. An increased incidence of focal erosions of the gastric mucosa and focal renal tubular basophilia were also seen.
Rat	1-Year with 6-Month Interim	25 F + 25 M	Oral	2,5,10,30,90*	At all doses, a decrease in weight gain (up to 16%) was observed. Serum urea nitrogen increased up to 4-fold; serum sodium decreased (average down to 3 mEq/L) and serum potassium increased (average up to 0.5 mEq/L). At 2, 5, 10 and 30 mg heart weight decreased; at 5, 10 and 30 mg, kidney weight increased; and at 5, 10, 30 and 90 mg, renal tubular basophilia increased. At 10, 30 and 90 mg, focal interstitial nephritis was observed.
Rat	3-Month with a 1-Month Interim and a 1-Month Recovery	30 F + 30 M	Oral	3,30,300,3000	At all doses, weight gain decreased by 5 to 11%, and increases were observed in serum urea nitrogen (up to approximately 3-fold) and serum potassium (average up to 0.4 mEq/L). At 30, 300 and 3000 mg there was an increased incidence of focal tubular basophilia persisted in rats given 300 or 3000 mg/kg/day.
Rat	1-Month	15 F + 15 M	Oral	30,60 30,60 (with saline)	Saline supplementation prevented decreased weight gain and elevations in serum urea nitrogen at 30 and 60 mg. Decreases in cardiac weight at 30 and 60 mg, were suppressed by saline supplementation in males at 30 mg. At 30 and 60 mg renal changes produced due to a low salt diet, (renal tubular degeneration and renal tubular basophilia) were prevented by saline supplementation. Mild gastric erosions or necrotic changes were seen in 1 or 2 of 30 rats given 30 or 60 mg. These gastric changes were not seen in saline supplemented animals given these doses; however, the relationship of amelioration due to saline is uncertain because of the low incidence of this change, which is also occasionally seen in untreated animals.
Rat	5 Days 6 Day Recovery	8 M	Oral	5, 300	Consumption of 2% saline increased during treatment at 5 mg and on Days 2 to 4 post-treatment at 300 mg.

* Dosing terminated Week 11, rats killed Week 27.

Subacute/Chronic Toxicology (continued)

Species	Duration	No. Of Animals/Group	Route	Dose mg/kg/day	Results
Dog	2-week	3 F + 3 M	Oral	3,10,30	At 30 mg, slight mineralization of the papilla muscle of the heart was seen in 1 of 6 dogs.
Dog	3-Month with 1-Month Interim	5 F + 5 M	Oral	3,10,30	At 10 mg, hemoglobin concentration, hematocrit, and erythrocyte count decreased in 2 dogs. Marked increases in serum urea nitrogen and creatinine were observed in 2 of 10 dogs. One of these dogs had marked renal tubular degeneration and ulcers of the tongue, gums, and gastric pyloric mucosa related to uremia. At 30 mg there was an increase in serum urea nitrogen (average up to 2-fold) and a decrease in serum sodium (down to 4 mEq/L) and serum chloride (down to 3 mEq/L). At 10 and 30 mg, average cardiac weight decreased (13 to 15%).
Dog	1-Year with 6-Month Interim	5 F + 5 M	Oral	3,5,15	At 15 mg, increases were observed in serum urea nitrogen (less than 2-fold). Decreases in serum sodium (average down to 2 mEq/L) and increases in serum potassium (average up to 0.5 mEq/L) occurred at all doses.
Dog	18-Day	3 F + 3 M	Oral	60/90 with and without saline	Saline supplementation prevented increases in serum urea nitrogen in dogs given 60 mg for 8 days followed by 90 mg for 8 or 9 days.
Dog	7-Day	4 F + 4 M	I.V.	60,90	Decreases in blood pressure and increases in serum urea nitrogen occurred in dogs given 60 or 90 mg/kg/day. Supplementation with physiologic saline (25 mL/kg one hour prior to dosing and 4 hours after dosing) prevented these changes. Increased serum potassium (average up to 0.6 mEq/L) anddecreased serum chloride (average down to 0.4 mEq/L) values were seen in both supplemented and unsupplemented animals.
Dog	1-Month	2 F + 2 M	Oral	3,30,300 and 1000	At 30 mg or greater, BUN increased and specific gravity of the urine decreased. Hyperplasia of renal epithelial cells was observed and deaths occurred. Dogs that died had dilation of distal renal tubules and fatty degeneration epithelium. No drug-related effects were observed at 3 mg.

Subacute/Chronic Toxicology (continued)

Species	Duration	No. Of Animals/Group	Route	Dose mg/kg/day	Results
Dog	3-Month with 1-Month Recovery (high dose)	Control 5 M + 5 F 3, 10 30 mg/kg/day 3 M + 3 F 100 mg/kg/day 8 M + 8 F Recovery Control 2 M + 2 F 100 mg/kg/day 5 M + 5 F	Oral	3,10,30 and 100	Eight of 16 dogs given 100 mg died or were killed because of poor physical condition. One of 6 dogs given 30 mg was killed because of poor physical condition. At 10 mg or greater increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible as only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.
Rabbit	2-Weeks	6 F	Oral	15 (1,6 & 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine, and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6, and 13 doses.

Teratology Studies

Species	No. Of Animals/Group	Dose mg/kg/day	Route	Duration of Dosing	Results
Mice	25	100,300,1000, 1000 with saline	Oral	Day 6 through Day 15 of gestation	No teratogenic effect was observed. There was an increased incidence of resorptions in all unsupplemented groups (no increase in serum urea nitrogen).
Rat	35	30,100,300, 300 with saline	Oral	Day 6 through Day 17 of gestation	No teratogenic effect was observed. Maternal effect was observed. Maternal weight gain decreased in all unsupplemented groups. The open field behavioral test (measure of spontaneous activity) showed increased activity in Week 5 postpartum F1 females at 300 mg with and without saline, but only in 300 mg with saline females in Week 6. When the open field test was repeated in males and females given 300 mg with and without saline in Week 11, no increase in activity was seen.
Rabbit (New Zealand)	18	0.1, 0.3, 1.0 all groups with saline	Oral	Day 6 through Day 18 of gestation	No teratogenic effect was observed. At all doses there was an increased incidence of incomplete ossification (sternebrae, metacarpals, forefoot phalanges, pelvic bones and tali and/or calcanea) which was considered to represent a fetotoxic effect. At 1 mg one rabbit had a high incidence of resorptions.
Rabbit (New Zealand)	18	0.031, 0.125, 0.5	Oral	Day 6 through Day 18 of gestation	No fetotoxicity, nor embryotoxicity was observed at maternotoxic doses. At 0.125 and 0.5 mg maternal deaths, decreased maternal weight gain and food consumption, as well as increases in BUN, creatinine and potassium were seen. In addition, doses of 0.5 mg produced decreases in serum sodium and chloride, diffuse distention of the renal distal tubules and degeneration of renal tubules.

Fertility and Late Gestation and Lactation with Postnatal Evaluation Studies

Species	No. Of Animals/Group	Route	Dose mg/kg/day	Duration of Dosing	Results
Rat	24 F & 24 M	Oral	30,100,300 300 with saline	Males were dosed for 78 days prior to mating and females from 15 days prior to mating until sacrifice on Day 20 of gestation	Weight gain was reduced in unsupplemented males at all doses and during gestation in unsupplemented females. No effects on fertility and no signs of teratogenicity were observed. There was an increase in F1 pup deaths (3 to 8% vs control 1%) Day 1 to 7 postpartum in 100 and 300 mg (saline and nonsaline) groups. Decreased mean F1 pup weight (3 to 7% less than controls) on Day 0 postpartum was seen in all unsupplemented groups.
Rat	20F	Oral	30,100,300 300 with saline	Day 15 of gestation through Day 21 postpartum	On Days 2 to 7 postpartum there was an increased number of dead pups (8 to 10% vs. Control 0%). On Day 21 postpartum, a decrease in pup weights (8% less than controls) was observed in the unsupplemented 100 and 300 mg groups. There was no effect in the supplemented group. Pup development was not altered.

Genotoxicity Studies

Study	Test System	Dose	Results
Mutagenesis Microbial mutagen with and without metabolic activation	Salmonella typhimurium TA1535, TA1537, TA98, TA100 Escherichia coli WP2, WP2 uvrA	up to 2000 fag/plate up to 10 mg/plate	Negative for mutagenic potential.
In vitro V-79 mammalian cell mutagenesis with and without metabolic activation	Chinese Hamster Lung Cell	up to 10 mM (4.42 mg/mL)	Negative for mutagenic potential.
DNA Damage In vitro alkaline elution	Rat Hepatocyte	up to 30 mM (13.25 mg/mL)	Negative for induction of DNA single strand breaks.
Chromosomal Evaluation In vitro chromosomal aberration assay with and without metabolic activation	Chinese Hamster Ovary	up to 30 mM (13.25 mg/mL)	Negative for induction of chromosomal aberration.
In vivo chromosomal aberration assay	Bone Marrow Cells of Male Mice	up to 5000 mg/kg	Negative for increases in chromosomal aberrations.

Carcinogenicity Studies

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
Mice Cri:CD-1 (ICR) BR	92 weeks	50 F & 50 M	Oral	15,45,135 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (7 to 15%) was seen in females at 135 mg. A greater incidence and severity of chronic nephritis in females and males given 45 and 135 mg was also seen.
Rats Cri:CD (SD) BR	105 weeks	50 F & 50 M	Oral	10,30,90 mg/kg/day	No evidence of carcinogenic effect was observed. Decreased weight gain (5 to 14%) in male drug- treated rats during the first 67 weeks of the study was observed. Focal sacculations of the retinal vessels was more prevalent in rats given 30 or 90 mg than in controls in Drug Week 100. An increased incidence of renal tubular hypertrophy in drug-treated males was seen at termination of the study (1 mg was considered the no-effect dose for this change in males based on an additional 105 week study at 1, 3, and 10 mg/kg/day). An increased incidence of chronic nephritis in drug-treated females (10 mg is the no-effect dose based on an additional 105 week study at 1, 3, and 10 mg/kg/day) was observed.

REFERENCES

1. Ajayi AA, Campbell BC, Howie CA, Reid JL. Acute and chronic effects of the converting enzyme inhibitors enalapril and lisinopril on reflex control of heart rate in normotensive man. J Hypertens 1985;3:47-53.

2. Biollaz J, Burnier M, Turini GA, Brunner DB, Porchet M, Gomez HJ, Jones KH, Feber F, Abrams WB, Gavras H, Brunner HR. Three new long-acting converting-enzyme inhibitors: relationship between plasma converting-enzyme activity and response to angiotensin I.Clin Pharmacol Ther 1981;29:665-670.

3. Biollaz J, Schelling JL, Jacot des Combes B, Brunner DB, Desponds G, Brunner HR, Ulm EH, Hichens M, Gomez HJ. Enalapril maleate and a lysine analogue (MK-521) in normal volunteers: Relationship between plasma drug levels and the renin angiotensin system. Br J Clin Pharmacol 1982;14:363-368.

4. Brunner DB, Desponds G, Biollaz J, Keller I, Feber F, Gavras H, Brunner HR, Schelling JL. Effect of a new angiotensin converting enzyme inhibitor MK-421 and its lysine analogue on the components of the renin system in healthy subjects. Br J Clin Pharmacol 1981;11:461-467.

5. Bussien JP, Waeber B, Nussberger J, Gomez HJ, Brunner HR.
Once-daily lisinopril in hypertensive patients: Effect on blood pressure and the renin-angiotensin system. Current Therapeutic Research 1985;37:342-351.

6. Chalmers JP, West MJ, Cyran J, De La Torre D, Englert M, Kramar M, Lewis GRJ, Maranhao MFL, Myburgh DP, Schuster P, Sialer S, Simon H, Stephens JD, Watson RDS.Placebo-controlled study of lisinopril in congestive heart failure: A multicenter study. J Card Pharmacol 1987;9(Suppl 3):S82-S88.

7. Chaturvedi N, Sjolie AK, Stephenson JM, Abrahamian H, Keipes M, Castellarin A, Rogulja-Pepeonik Z, Fuller JH, the EUCLID Study Group. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes.Lancet 1998;351:28-31.

8. Cirillo VJ, Gomez HJ, Salonen J, Salonen R, Rissanen V, Bolognese JA, Nyberg R, Kristianson K. Lisinopril: dose-peak effect relationship in essential hypertension.
Br J Clin. Pharmac 1988;25:533-538.

9. Derkx FHM, Millar JA, Reid JL, Schalekamp MADH. Pharmacodynamics of MK421 (enalapril) and its lysine analogue MK521. Progress in Pharmacol 1984;5:93-105.

10. Donohue JF, Kelly J, Laher MS, Doyle GD. Lisinopril in the treatment of hypertensive patients with renal impairment. Am J Med 1988;85(Suppl 3B):31-34.

11. Giles TD, Katz R, Sullivan JM, Wolfson P, Haugland M, Kirlin P, Powers E, Rich S, Hackshaw B, Chiaramida A, Rouleau JL, Fisher MB, Pigeon J, Rush JE. Short- and long-acting

angiotensin-converting enzyme inhibitors: A randomized trial of lisinopril versus captopril in the treatment of congestive heart failure. J Am Coll Cardiol 1989;13(6):1240-1246.

12. GISSI-3 Gruppo Italiano per lo Studio della Sopravvivenza ell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994;343:1115-1122.

13. Laher MS, Natin D, Rao SK, Jones RW, Carr P. Lisinopril in elderly patients with hypertension. J Card Pharmacol 1987;9(Suppl 3) S69-S71.

14. Massie BM, Cleland GFJ, Armstrong PW, Packer M, Poole-Wilson PA, Ryden L, for the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial investigators. Regional differences in the characteristics and treatment of patients participating in an international heart failure trial. Journal of Cardiac Failure 1998;4:3-8.

15. Millar JA, Derkx FHM, McLean K, Reid JL. Pharmacodynamics of converting enzyme inhibition: The cardiovascular endocrine and autonomic effects of MK-421 (enalapril) and MK-521. Br J Clin Pharmacol 1982;14:347-355.

16. Myers MG, Carruthers SG, Leenen FHH, Haynes RB. Recommendations from the Canadian Hypertension Society Consensus Conference on the pharmacologic treatment of hypertension. CMAJ 1989;140:1141-1146.

17. Powers ER, Chiaramida A, DeMaria AN, Giles TD, Hackshaw B, Hart W, Haugland M, Johnston R, Katz R, Kirlin P, McCall M, Mohiuddin S, Rich S, Sullivan JM, Wolfson P and Co-investigators. A double-blind comparison of lisinopril with captopril in patients with symptomatic congestive heart failure. J Card Pharmacol 1987;9(Suppl 3):S82-S88.

18. Product Monograph for Zestril® (lisinopril) 5 mg, 10 mg and 20 mg tablets, Date of Revision: November 10, 2006.

19. Rotmensch HH, Vlasses PH, Swanson BN, Irvin JD, Harris KE, Merrill DD, Ferguson RD. Antihypertensive efficacy of once daily MK-521, a new nonsulfhydryl angiotensin-converting enzyme inhibitor. Am J Cardiol 1984;53(1):116-119.

PART III: CONSUMER INFORMATION

MINT-LISINOPRIL
lisinopril tablets

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

ABOUT THIS MEDICATION

What the medication is used for:
MINT-LISINOPRIL is used for the treatment of high blood pressure and heart failure (a condition where the heart cannot pump adequate amounts of blood to satisfy the needs of the body). MINT-LISINOPRIL is also used to improve survival after a heart attack.

What it does:
Lisinopril is in a class of medications called angiotensin -converting enzyme (ACE) inhibitor. Its main action is to lower blood pressure by preventing the effects of angiotensin II (a chemical that narrows the blood vessels). By blocking angiotensin II effects, the blood vessels relax, letting the blood flow more smoothly, thereby lowering the blood pressure.

When it should not be used:
Do not use MINT-LISINOPRIL if:

- you are allergic to lisinopril or any other component in the product or the container (see *What the important non-medicinal ingredient are*),
- you are allergic to any other medication in the same class called angiotensin-converting enzyme (ACE) inhibitors such as enalapril, captopril, quinapril, ramipril etc.,
- you have a history of angioedema (angioneurotic edema), a condition that causes swelling of the face, extremities, eyes, lips, tongue, difficulty in breathing after taking an angiotensin-converting enzyme (ACE).
- you have been diagnosed with hereditary angioedema or idiopatic angioedema (angioedema of unknown cause).

What the medicinal ingredient is:
Lisinopril as lisinopril dihydrate.

What the important non-medicinal ingredients are:
corn starch, dibasic calcium phosphate (anhydrous), magnesium stearate, mannitol, pregelatinized starch and red iron oxide.

What dosage forms it comes in:
Tablets, 5 mg, 10 mg and 20 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
MINT-LISINOPRIL should not be used during pregnancy. Stop the medication and contact your physician as soon as possible, if you discover that you are pregnant while taking MINT-LISINOPRIL.

BEFORE you use MINT-LISINOPRIL, talk to your physician or pharmacist if:

- You are pregnant. Taking MINT-LISINOPRIL during pregnancy can cause injury and even death to your baby.
- You are breast-feeding. It is possible that MINT-LISINOPRIL passes into the breast milk. You should not breast-feed while taking MINT-LISINOPRIL.
- You suffer from low blood pressure.
- You have any of these conditions:
  - diabetes
  - heart or blood vessel disease
  - liver disease
  - kidney disease
- You are vomiting.
- You have diarrhea
- You are going to have any surgery.
- You want to use any potassium supplements or salt substitutes containing potassium.
- You find that you are excessively sweating and feel dehydrated.
- You have any allergies to this drug or its ingredients or components of the container.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with MINT-LISINOPRIL include: other medicines used to reduce blood pressure, acetyl salicylic acid (Aspirin®) and other non-steroidal anti-inflammatory medications (NSAIDs) such as indomethacin; diuretics (water pills) ; lithium; potassium supplements;salt substitutes that contain potassium; medicines that contains potassium; insulin or oral antidiabetic agents such as glimepiride and certain medications that tend to increase pressure, such as, non-

prescription preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems.

PROPER USE OF THIS MEDICATION

Usual dose:
Based on your condition, your doctor will decide the usual dose of MINT-LISINOPRIL you need to take.

MINT-LISINOPRIL is not affected by food. As such, you can take the tablets before, during or after meals.

MINT-LISINOPRIL should be taken in one dose once a day. It should be taken at the same time each day.

Overdose:
It is important to follow the instructions from your doctor or pharmacist. If you or someone have taken more than the recommended dose at once contact your doctor or nearest hospital emergency department immediately.

Missed Dose:
If a dose of this medication is missed, it should be taken as soon as possible. This will help to keep a constant amount of medication in the blood. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Symptom / effect		Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Common	Fatigue	✓		
	Dizziness/ Lightheadedness	✓		
	Hypotension		✓	
	Headache	✓		
	Rash/itching		✓	
	Nausea/Vomiting/ Diarrhea	✓		
	Cough		✓	
	Chest pain		✓	
	Dyspnea		✓	
	Sore Throat		✓	
Uncommon	Allergic reactions/ Angioedema			✓
	Flu-like symptoms (such as fever, malaise, muscle pain)		✓	
	Liver impairment such as jaundice, dark/brown urine		✓	
	Abdominal pain	✓		
	Loss of appetite	✓		
	Fainting			✓

If you notice any of the following, you may need medical attention.

- Symptoms of angioedema such as: sudden difficulty in breathing or swallowing, swelling of face, eyes, lips, tongue and/or throat, hands or feet. The black patients are at increased risk of these types of reactions to ACE inhibitors.
- Dizziness, lightheadedness or fainting following exercise, and/or when it is hot and you have lost a lot of water by sweating.
- Flu-like symptoms such as fever, malaise, muscle pain, rash, itching, abdominal pain, nausea, vomiting, diarrhea, jaundice, loss of appetite.

- The initial dose may cause a greater fall in blood pressure than will occur following continued treatment. You may notice this as faintness or dizziness and it may help to lie down. If concerned, please consult your physician or pharmacist.
- Dry cough, sore throat.
- Unusual tiredness and/or weakness
- Headache

Your ability to drive and use machines may be hampered as you may feel dizzy or tired while taking MINT-LISINOPRIL.

Contact your physician or pharmacist if you notice any of the above or have other side effects. Seek medical attention, if the condition persists or worsens.

This is not a complete list of side effects. For any unexpected effects while taking MINT-LISINOPRIL contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 - 30ºC). Protect from light.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.mintpharmaceuticals.ca or by contacting the sponsor, Mint Pharmaceuticals Canada Inc. at: 1.905.271.9696.

This leaflet was prepared by Mint Pharmaceuticals Canada Inc.

Last revised: September 29, 2008