

PRODUCT MONOGRAPH

Pr ***RIVA-LISINOPRIL***

Lisinopril Tablets, USP

5 mg, 10 mg and 20 mg
(of Lisinopril as Lisinopril Dihydrate)

Angiotensin Converting Enzyme Inhibitor

Laboratoire Riva Inc.
660 Boul. Industriel
Blainville, Quebec
Canada, J7C 3V4

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RIVA-LISINOPRIL

Lisinopril Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablets, 5 mg, 10 mg, 20 mg (of lisinopril as lisinopril dihydrate)	<i>RIVA-LISINOPRIL</i> (lisinopril) does not contain any clinically relevant nonmedicinal ingredients. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

RIVA-LISINOPRIL (lisinopril) is indicated for:

- Treatment of essential hypertension and in renovascular hypertension
- Management of symptomatic congestive heart failure as adjunctive treatment with diuretics and, where appropriate, digitalis.
- Treatment of hemodynamically stable patients as early as within 24 hours following acute myocardial infarction, to improve survival.

Hypertension

RIVA-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. *RIVA-LISINOPRIL* has been used concomitantly with beta-blockers and calcium antagonists, but the data on such use are limited.

RIVA-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. *RIVA-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

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

High doses of 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

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

RIVA-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 WARNINGS AND PRECAUTIONS, Hypotension Following Acute Myocardial Infarction, Renal Impairment).

General

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

Pregnancy

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, *RIVA-LISINOPRIL* should be discontinued as soon as possible.

Geriatrics (≥ 65 years of age):

Evidence from clinical studies and experience suggest that use in the geriatric population is associated with differences in safety or effectiveness and a brief discussion can be found in the appropriate sections (e.g. Clinical Trials, Pharmacology, Warnings and Precautions).

Pediatrics:

Safety and effectiveness in children have not been established.

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, Angiotensin Converting Enzyme (ACE) inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, *RIVA-LISINOPRIL* should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Carcinogenesis and Mutagenesis

See TOXICOLOGY for discussion on animal data.

Cardiovascular

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, *RIVA-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 nonblack patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk

of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: 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-dependent 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 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 lisinopril discontinuation (see ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION, 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 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.

Lisinopril should be given with caution to these patients.

Endocrine and Metabolism

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 lisinopril (See DRUG INTERACTIONS).

Hyperkalemia: In clinical trials with daily doses of 2.5 mg 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 hyperkalemia (6.4% vs 3.5%). This event was manageable and rarely led to treatment withdrawal. Therapy discontinuation rates due to hyperkalemia 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 lisinopril who develop jaundice or marketed elevation of hepatic enzymes should discontinue lisinopril and receive appropriate medical follow-up (See PRECAUTIONS – Patients with Impaired Liver Function).

Should the patient receiving lisinopril experience any unexplained symptoms (see Information for Patients), 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 lisinopril should be considered when appropriate.

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

Immune

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

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.

Occupation Hazards

Ability to drive and use machines: dizziness or tiredness may occur during treatment with lisinopril.

Renal

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 lisinopril (serum creatinine concentration exceeding 265 micromol/L or a doubling from the pre-treatment value), then the physician should consider withdrawal of lisinopril.

Use of 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, *RIVA-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 towards 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.

Use in Nursing Mothers

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

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.

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. Pharmacokinetics 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 (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

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.

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.

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 I.

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

		Hypertension n= 2633 Patients (%)	Congestive Heart Failure n= 636 Patients (%)
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

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

		Hypertension n= 2633 Patients (%)	Congestive Heart Failure n= 636 Patients (%)
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
	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, Cardiovascular, 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:

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

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Event	Control n=4729	Lisinopril n=4713	Lisinopril + GTN n=4722	GTN alone n=4731
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

Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see WARNINGS AND PRECAUTIONS).

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). 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 causes of anemia. Rarely, hemolytic anemia has been reported.

Agranulocytosis and bone marrow depression, manifested as anemia, cytopenia or leukopenia, 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).

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 ($\geq 10\%$), common ($\geq 1\%$, $< 10\%$), uncommon ($\geq 0.1\%$, $< 1\%$), rare ($\geq 0.01\%$, $< 0.1\%$), 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, Neutropenia/Agranulocytosis).

Metabolism and nutrition disorders

Uncommon: hyperkalemia (see WARNINGS AND PRECAUTIONS, Hyperkalemia).
Rare: hyponatremia.
Very rare: hypoglycaemia (see WARNINGS AND PRECAUTIONS, 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, Hypotension).
Uncommon: myocardial infarction or cerebrovascular accident (both possibly secondary to excessive hypotension in high risk patients (see WARNINGS AND PRECAUTIONS, 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, Hypersensitivity/Angioedema and ADVERSE EVENTS, 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 marked elevation of hepatic enzymes should discontinue lisinopril and receive appropriate medical follow-up (See WARNINGS AND PRECAUTIONS, Patients with Impaired Liver Function).

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritus.
Rare: hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis, and/or larynx (See WARNINGS AND PRECAUTIONS, Hypersensitivity/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), eosinophilia 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, Patients with Impaired Liver Function).

Rare: decreases in hemoglobin, decreases in hematocrit, increases in serum bilirubin (see WARNINGS AND PRECAUTIONS, 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 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 lisinopril.

Lithium Salts:

As with other drugs which eliminate sodium, the 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

There is no clinically significant effect of food on the bioavailability of lisinopril (see DOSAGE AND ADMINISTRATION).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Since absorption of lisinopril is not affected by food, the tablets may be administered before, during or after meals. lisinopril should be administered in a single daily dose. lisinopril should be taken at the same time each day.

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

Recommended Dose and Dosage Adjustment

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 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 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 lisinopril. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with lisinopril to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS). The dosage of lisinopril should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with 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).

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).

Geriatrics: 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 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: 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 lisinopril, because severe hypotension and, more rarely, consequent renal failure have been reported (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and 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 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 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 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 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), lisinopril should be withdrawn.

Renal function should be assessed before and during therapy with lisinopril (see WARNINGS

AND PRECAUTIONS, Renal Impairment).

Dosing should normally continue for 6 weeks. At that time, patients with signs or symptoms of heart failure should continue with lisinopril (see DOSAGE AND ADMINISTRATION, Congestive Heart Failure).

Lisinopril is compatible with intravenous or transdermal glyceryl trinitrate.

Missed Dose

The missed dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should be taken. Doses should not be doubled.

Administration

Lisinopril tablets are intended to be taken orally.

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, 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).

SD

ACE is identical to kininase II. Thus, lisinopril may also block the degradation of bradykin, 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.

Pharmacodynamics

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 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) \leq 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 a 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.

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

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

Metabolism and Excretion: 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).

Special Populations and Conditions

Pediatrics: No data available.

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.

Gender: No data available.

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

Hepatic Insufficiency: See WARNING AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

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

Lisinopril can be removed by dialysis.

Genetic Polymorphism: No data available.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form:

RIVA-LISINOPRIL 5 mg tablets are pink, round, biconvex tablets marked "L" scoreline "5" on one side and "S" on the other side.

RIVA-LISINOPRIL 10 mg tablets are pink, round, biconvex tablets marked "L" scoreline "10" on one side and "S" on the other side.

RIVA-LISINOPRIL 20 mg tablets are pink, round, biconvex tablets with “L” scoreline “20” on one side and “S” on the other side.

Composition:

Each tablet contains either 5 mg, 10 mg or 20 mg of lisinopril as lisinopril dihydrate as the active ingredient, and the following non-medicinal ingredients: calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, magnesium stearate, maize starch, mannitol, pregelatinized starch and red iron oxide.

Packaging:

RIVA-LISINOPRIL tablets are available in bottles of 100 and 500 tablets, and blister packages of 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

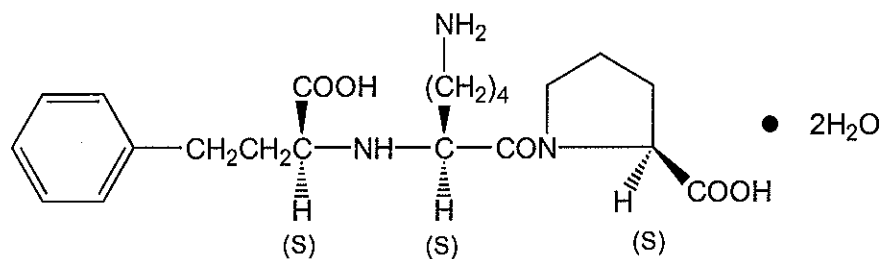
Proper name: Lisinopril

Chemical name: 1-[N²-[(S)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate

Molecular formula: C₂₁H₃₁N₃O₅ • 2H₂O

Molecular mass: 441.52

Structural formula:



Physicochemical

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

CLINICAL TRIALS

A blinded, single-dose, randomized, two-period, two-sequence, two-treatment, crossover comparative bioavailability study of *RIVA-LISINOPRIL* (lisinopril) 20 mg tablets against the Canadian Reference Product, Lisinopril® 20 mg tablets, has been performed on healthy volunteers under fasting conditions. A summary of the bioavailability data is presented in Table II.

Table II: Comparative Bioavailability Data for *RIVA-LISINOPRIL* (lisinopril) 20 mg vs. Lisinopril® 20 mg tablets (Uncorrected for Potency)

<p>Lisinopril (1 x 20 mg) From measured data</p> <p>Geometric Mean Arithmetic Mean (CV %)</p>
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Parameters*	Lisinopril 20 mg Tablets	Lisinopril® 20 mg Tablets†	% Ratio of Geometric Means	90% Confidence Interval
AUC ₀₋₇₂ (ng•h/mL)	1127.64 1194.75 (33)	1076.48 1120.01 (30)	104.75	96.54 - 113.66
C _{MAX} (ng/mL)	79.52 85.48 (37)	76.59 81.18 (37)	103.83	94.92 - 113.56
T _{MAX} § (h)	6.16 (17)	6.19 (20)		

† Lisinopril® (AstraZeneca Canada Inc.) was manufactured and purchased in Canada.

§ Expressed as the arithmetic mean (CV%) only.

* Due to the design of the study, meaningful AUC_t and t_{1/2} parameters could not be calculated.

DETAILED PHARMACOLOGY

Mechanism of Action

Study	Species/Strain	Number of Animals/ Group	Route	Dose	Results
<i>in vitro</i> ACE inhibitory activity*	hog plasma		<i>in vitro</i>		IC ₅₀ = ± 0.5 nM
augmentation of contractile response to bradykinin	guinea pig ileum	7 segments	<i>in vitro</i>		AC ₅₀ = 1.6 nM
<i>in vivo</i> ACE inhibition in the rat**	male Sprague/Dawley	8	i.v.		ID ₅₀ = 2.3 (1.7-3.1) µg/kg
duration of ACE inhibitory activity of lisinopril in rats**	male Sprague/Dawley	4	i.v.	3 & 10 µg/kg	Duration approx. 110 min.
<i>in vivo</i> 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 min.
<i>in vivo</i> ACE inhibition in anesthetized dogs**	mongrel	6	i.v.	1-30 µg/kg	ID ₅₀ = 6.5 µg/kg
<i>in vivo</i> 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 ¹⁴C labeled substrate.

** Blockage of functional (pressor) response to A1 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 hydrochlorothiazide	After 2 hours: Lisinopril alone: 5% reduction in mean systolic pressure vs pretreatment. Lisinopril + HCTZ = 11% reduction in mean systolic pressure vs pretreatment.
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 pre-treatment 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 ½ - 18 hours.

MICROBIOLOGY

No data available.

TOXICOLOGY

Acute Toxicity of Lisinopril

LD₅₀ 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 toxicity 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 toxicity or death occurred in the males.

Subacute/Chronic Toxicology

Species	Duration	No. of Animals/ Groups	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 to 10%) 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 ^a	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 renal tubular basophilia persisted in rats given 300 or 3000 mg/kg/day.

^a Dosing terminated Week 11, rats killed Week 27.

Subacute/Chronic Toxicology (continued)

Species	Duration	No. of Animals/ Groups	Route	Dose mg/kg/day	Effects
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.
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 was decreased (13 to 15%).

Subacute/Chronic Toxicology (continued)

Species	Duration	No. of Animals/ Groups	Route	Dose mg/kg/day	Effects
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) and decreased 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 of renal tubular epithelium. No drug-related effects were observed at 3 mg.
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.

Species	Duration	No. of Animals/ Groups	Route	Dose mg/kg/day	Effects
Rabbit	2-Week	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 (sternbrae, 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 or 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	20 F	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	<i>Salmonella typhimurium</i> TA1535, TA1537, TA98, TA100 <i>Escherichia coli</i> WP2, WP2 uvrA	up to 2000 µg/plate up to 10 mg/plate	Negative for mutagenic potential.
<i>In vitro</i> 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			
<i>In vitro</i> alkaline elution	Rat Hepatocyte	up to 30 mM (13.25 mg/mL)	Negative for induction of DNA single strand breaks
Chromosomal Evaluation			
<i>In vitro</i> 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
<i>In vivo</i> 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	Effects
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 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.

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PART III: CONSUMER INFORMATION

RIVA-LISINOPRIL
(Lisinopril Tablets, USP)

This leaflet is part III of a three-part "Product Monograph" published when *RIVA-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 *RIVA-LISINOPRIL*. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

RIVA-LISINOPRIL is the brand name of Laboratoire Riva Inc. for the substance - lisinopril, available **only on prescription** from your physician. Lisinopril is one of a class of medicines known as angiotensin-converting enzyme (ACE) inhibitors.

RIVA-LISINOPRIL is usually prescribed to:

- Reduce high blood pressure.
- Treat patients with heart failure

Remember - This medicine is prescribed for the particular condition that you have. **Do not give this medicine to other people, nor use it for any other condition.**

What it does:

RIVA-LISINOPRIL belongs to a class of medicines known as angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors work mainly by blocking an enzyme in the body that is necessary to produce angiotensin II, a substance that causes blood vessels to constrict (tighten). As a result, ACE inhibitors indirectly relax blood vessels which lowers blood pressure.

After taking a dose of *RIVA-LISINOPRIL*, the blood pressure lowering effect will be seen after 1 hour, with peak reduction of blood pressure usually achieved by 6 hours after dosing. In some patients, achievement of optimal blood pressure reduction may require 2 to 4 weeks of therapy.

When it should not be used:

- If you have any allergies to lisinopril or to any other ingredients in *RIVA-LISINOPRIL*. (See What the important nonmedicinal ingredients are).
- You have previously taken lisinopril or other medications of the same type - angiotensin-converting enzyme (ACE) inhibitors, and you were allergic or reacted badly to it, particularly if you experienced swelling of the face, lips, tongue, or throat, or had sudden difficulty breathing or swallowing. These drugs usually have names ending with 'pril' such as lisinopril, enalapril, captopril, etc. You should not take *RIVA-LISINOPRIL* if you had these types of reactions without a known cause.
- If you have been diagnosed with angioedema, including laryngeal edema and, may occur especially following the first dose of lisinopril. You should report immediately any signs of symptoms suggesting angioedema (swelling of face,

extremities, eyes, lips, tongue, difficulty in breathing) and to take no more drug until you have been consulted with the prescribing physician.

- If you have been diagnosed with hypotension, you should report light headedness especially during the first few days of therapy. If actual syncope occurs, you should discontinue the drug until you have been consulted with the prescribing physician.
- If you are pregnant or breast-feeding.
- If you impaired renal functions.

What the medicinal ingredient is:

Lisinopril dihydrate

What the important nonmedicinal ingredients are:

Calcium hydrogen phosphate dihydrate, colloidal anhydrous silica, magnesium stearate, maize starch, mannitol, pregelatinized starch and red iron oxide.

What dosage forms it comes in:

RIVA-LISINOPRIL are available as 5 mg, 10 mg and 20 mg tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

***RIVA-LISINOPRIL* should not be used during pregnancy. If you discover that you are pregnant while taking *RIVA-LISINOPRIL*, stop the medication and please contact your doctor as soon as possible.**

This medicine may not be suitable for certain people. **BEFORE** you use *RIVA-LISINOPRIL* talk to your doctor or pharmacist if:

- You have previously taken lisinopril or other ACE inhibitors and you were allergic or reacted badly to it.
- **You are pregnant, breast-feeding or thinking of becoming pregnant.** Taking *RIVA-LISINOPRIL* during pregnancy can cause injury and even death to your developing baby. This medicine should not be used during pregnancy. If you become pregnant while taking *RIVA-LISINOPRIL*, stop the medication and report to your physician as soon as possible. It is possible that *RIVA-LISINOPRIL* passes into breast milk. You should not breast-feed while taking *RIVA-LISINOPRIL*.
- You have any of these conditions:
 - diabetes
 - heart or blood vessel disease
 - liver disease
 - kidney disease and/or are on dialysis
 - a history of angioedema
 - renal impairment
- You are taking any other medication, whether on prescription or otherwise.
- You are vomiting or have severe diarrhea.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with *RIVA-LISINOPRIL* include:

- diuretics or "water pills"
- any other medicines to reduce blood pressure
- potassium supplement, potassium-sparing agents or potassium-containing salt substitutes
- Agents causing rennin release, e.g. diuretics
- lithium salts
- non-steroidal anti-inflammatory drug (NSAIDs), e.g. indomethacin
- Agents affecting sympathetic activity, e.g. ganglionic blocking agents or adrenergic neuron blocking agents and beta-adrenergic blocking drugs
- antidiabetics

PROPER USE OF THIS MEDICATION

Usual dose:

Since absorption of *RIVA-LISINOPRIL* tablets (lisinopril) is not affected by food, the tablets may be administered before, during or after meals. *RIVA-LISINOPRIL* should be administered in a single daily dose. *RIVA-LISINOPRIL* should be taken at the same time every day.

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

Overdose:

In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. The most likely symptom of overdose include severe hypotension, electrolyte disturbances, and renal failure.

Missed Dose:

If you miss a dose of this medicine, take it as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should be taken. **Do not take a double dose.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including lisinopril, may cause side effects. Most people do not experience any problem when taking this medicine; but if you notice any of the following, medical attention may be needed.

You may experience some side effects such as:

- Dizziness.
- Cough
- Diarrhea
- Headache
- asthenia/fatigue
- Nausea
- Rash
- Vomiting

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 call your doctor or pharmacist
		Only if severe	In all cases	
Common	Hypotension (excessive fall in blood pressure)*		✓	
	Unusual tiredness/weakness	✓		
Uncommon	Allergic reactions - Angioedema (Swelling of face, eyes, lips, tongue and/or throat, hands or feet)** - Sudden difficulty in breathing or swallowing			✓
	Impaired liver function (symptoms: jaundice, i.e. yellowing of skin or the whites of the eye; abdominal pain)		✓	
	Signs of infection or flu-like symptoms (e.g., sore throat, fever, muscle pain, abdominal pain, loss of appetite)	✓		

* 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.

** You should be aware that black patients are at increase risk of these types of reactions to ACE inhibitors.

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

HOW TO STORE IT

Store your tablets at 15°C-30°C, in a tightly closed container, away from heat and direct light, and out of damp places, such as the bathroom or kitchen.

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: cadtmp@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 by contacting the sponsor, Laboratoire Riva Inc., at: 1-800-363-7988

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