PRODUCT MONOGRAPH

ratio-LISINOPRIL P

Lisinopril

Tablets 5 mg, 10 mg and 20 mg

USP

Angiotensin Converting Enzyme Inhibitor

ratiopharm inc.
Canada J7J 1P3

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 5 mg, 10 mg, and 20 mg	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

ratio-LISINOPRIL P should normally be used in those patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects. ratio-LISINOPRIL P 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
ratio-LISINOPRIL P is indicated in the management of symptomatic congestive heart failure as adjunctive treatment with diuretics and, where appropriate, digitalis. Treatment with ratio-LISINOPRIL P should be initiated under close medical supervision, usually in a hospital.

Treatment Following Acute Myocardial Infarction
ratio-LISINOPRIL P 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 ratio-LISINOPRIL P should be reassessed after six weeks. If there is no evidence of symptomatic or asymptomatic left ventricular dysfunction, treatment with ratio-LISINOPRIL

P can be stopped.

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

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

CONTRAINDICATIONS

ratio-LISINOPRIL P (lisinopril) is contraindicated in patients who:

- are hypersensitive to any component of this product (for a complete listing, see the Dosage forms, composition and packaging section of the product monograph);
- have a history of angioneurotic edema relating to previous treatment with an angiotensin-converting enzyme inhibitor;
- have hereditary or idiopathic angioedema.

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, ratio-LISINOPRIL P should be discontinued as soon as possible.

Angioedema

Angioedema has been reported in patients treated with Lisinopril. This may occur at any time during treatment. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema occurs, ratio-LISINOPRIL P should be promptly discontinued and the patient should be observed until the swelling subsides. Where swelling is confined to the face, lips and mouth the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, 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).

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 doses of ratio-LISINOPRIL P and/or reduced concomitant diuretic therapy should be considered.

If hypotension occurs during treatment following acute myocardial infarction, consideration should be given to ratio-LISINOPRIL P 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 ratio-LISINOPRIL P. If hypotension occurs, a reduction of dose or discontinuation of therapy should be considered.

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.

Use in Pregnancy
ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, ratio-LISINOPRIL P 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 with some clinical benefit and may, theoretically be removed by exchange transfusion, although there is no experience with the latter procedure.

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 labelled 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.

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 μmol/L and/or proteinuria exceeding 500 mg/24 hour. If renal dysfunction develops during treatment with ratio-LISINOPRIL P (serum creatinine concentration exceeding 265 μmol/L or a doubling from the pre-treatment value), then the physician should consider withdrawal of ratio-LISINOPRIL P.

Use of ratio-LISINOPRIL P should include appropriate assessment of renal function.

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 three 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 patients treated with placebo.

Hyperkalemia
In clinical trials 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. 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).

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.

ratio-LISINOPRIL P should be given with caution to these patients.

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.

Patients with Impaired Liver Function
Hepatitis, jaundice (hepatocellular and/or cholestatic), 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). In most cases the changes were reversed on discontinuation of the drug.

Should the patient receiving ratio-LISINOPRIL P 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 ratio-LISINOPRIL P should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ratio-LISINOPRIL P should be used with particular caution in patients with pre-existing liver abnormalities. In such patients, baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

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

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

Use 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 (see DOSAGE AND ADMINISTRATION).

Pediatric Use
Safety and effectiveness in children have not been established.

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

Anaphylactoid Reactions during LDL Apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid Reactions during Hymenoptera Desensitization
There have been isolated reports of patients experiencing sustained life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasp) 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.

ADVERSE REACTIONS

In controlled clinical trials involving 3269 patients (2633 patients with hypertension and 636 patients with congestive heart failure), 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 tablets in controlled clinical trials, comparative incidence data are listed in the table below.

INCIDENCE OF ADVERSE REACTIONS
OCCURRING IN PATIENTS TREATED WITH LISINOPRIL
IN CONTROLLED CLINICAL TRIALS

	HYPERTENSION (2633 PATIENTS) %	CONGESTIVE HEART FAILURE (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
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%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with ratio-LISINOPRIL P should be discontinued and appropriate therapy instituted immediately (see WARNINGS AND PRECAUTIONS, Angioedema).

In very rare cases intestinal angioedema has been reported with angiotensin-converting enzyme inhibitors including lisinopril.

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).

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.

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 at 6 weeks were as follows:

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

Other Events in Controlled Clinical Trials or Post-Marketing Experience.
Additional adverse reactions which were reported rarely, either during controlled clinical trials or after the drug was marketed, include:

Cardiovascular
- Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see WARNINGS AND PRECAUTIONS, Hypotension)
- Tachycardia

Dermatologic
- Alopecia
- Diaphoresis
- Pruritis
- Urticaria

Severe Skin Disorders
- Erythema multiforme
- Pemphigus
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Gastrointestinal
- Abdominal pain and indigestion
- Dry mouth
- Pancreatitis
- Vomiting

Hematologic
- Hemolytic anemia

Hepatic
- Hepatitis
- Jaundice (hepatocellular and/or cholestatic)
- Liver function abnormalities

Nervous System
- Mental confusion
- Mood alterations
- Paresthesia
- Vertigo

Respiratory
- Bronchospasm
- Rhinitis
- Sinusitis

Special Senses
- Taste disorders

Urogenital
- Acute renal failure
- Impotence
- Oliguria/anuria
- Renal dysfunction
- Uremia

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity, or other dermatologic manifestations may also occur.

Laboratory Test Findings

Serum Electrolytes
Hyperkalemia and hyponatremia have occurred (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). Reversible increases in blood urea nitrogen (14.5%) and serum creatinine (11.2%) were observed in approximately 12.0% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Hematology
Decreases in hemoglobin and hematocrit (mean decreases of approximately 0.9 g percent and 0.6

vol percent, 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, thrombocytopenia 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, 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%).

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, Hypotension and DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium
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 ratio-LISINOPRIL P 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
The antihypertensive effect of lisinopril may be diminished with concomitant nonsteroidal anti-inflammatory drug use. In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, the co-administration of ACE inhibitors may result in further deterioration of renal function.

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

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.

DOSAGE AND ADMINISTRATION

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

Dosage must be individualized.

Essential Hypertension
In patients with essential hypertension, not on diuretic therapy, the usual recommended starting dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response: the usual dosage range is 10 to 40 mg per day, administered in a single daily dose. In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy. 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 ratio-LISINOPRIL P alone, a low dose of a diuretic may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of ratio-LISINOPRIL P.

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of ratio-LISINOPRIL P. The diuretic should be discontinued, if possible, for two to three days before

beginning therapy with ratio-LISINOPRIL P to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS). The dosage of ratio-LISINOPRIL P should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with ratio-LISINOPRIL P 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, 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**
≤ 70 ≥ 30 mL/min (≤ 1.17 ≥ 0.5 mL/s)	5.0 - 10.0 mg/day
≤ 30 ≥ 10 mL/min (≤ 0.5 ≥ 0.17 mL/s)	2.5 -5.0 mg/day
< 10 mL/min (< 0.17 mL/s) (including patients on dialysis)	2.5 mg/day[x]

[x] 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 treated concomitantly with an ACE inhibitor) (see WARNINGS AND PRECAUTIONS, 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 ratio-LISINOPRIL P. 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 ratio-LISINOPRIL P. Therefore, a lower starting dose of 2.5 or 5 mg is recommended. Thereafter, the dosage may be adjusted according to the blood pressure response.

Congestive Heart Failure
ratio-LISINOPRIL P is to be used in conjunction with a diuretic 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 ratio-LISINOPRIL P, because severe hypotension and, more rarely, consequent renal failure have been reported (see WARNINGS AND PRECAUTIONS, 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. If required, the dose should be increased gradually, depending on the patient response. The usual effective dosage range is 5-20 mg per day administered in a single daily dose. Dose titration may be performed over a 2-4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure.

Treatment Following Acute Myocardial Infarction
Treatment of hemodynamically stable patients may be started as early as within 24 hours following the onset of symptoms of myocardial infarction. Patients should receive, as appropriate, standard recommended treatments (see INDICATIONS AND CLINICAL USE, Treatment Following Acute Myocardial Infarction)**.**

The first dose of ratio-LISINOPRIL P 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 three days after the infarct should be given a lower dose, 2.5 mg orally. Treatment with ratio-LISINOPRIL P must not be initiated in patients who are at risk of serious hemodynamic deterioration (see WARNINGS AND PRECAUTIONS, 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 one hour), ratio-LISINOPRIL P should be withdrawn.

Renal function should be assessed before and during therapy with ratio-LISINOPRIL P (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 ratio-LISINOPRIL P (see DOSAGE AND ADMINISTRATION, Congestive Heart Failure).

ratio-LISINOPRIL P is compatible with intravenous or transdermal glyceryl trinitrate.

OVERDOSAGE

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. If available, angiotensin II may be beneficial.

Lisinopril may be removed from the general circulation by hemodialysis. (see WARNINGS AND PRECAUTIONS, Anaphylactoid Reactions during Membrane Exposure).

ACTION AND CLINICAL PHARMACOLOGY

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

Angiotensin-converting enzyme 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.

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 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 six 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 six 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.

The antihypertensive effect of angiotensin-converting enzyme inhibitors is generally lower in black than in non-black patients.

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.

Pharmacokinetics

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 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). 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.

In a study in elderly healthy subjects (65 years and above), a single dose of lisinopril 20 mg produced higher serum concentrations 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.

The elimination of lisinopril in patients with renal insufficiency is similar to that in patients with normal renal function until the glomerular filtration rate is 30 mL/min or less. With renal function ≤30 mL/min, peak and trough lisinopril levels increase, time to peak concentration increases and time to steady state is prolonged (see DOSAGE AND ADMINISTRATION).

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

STORAGE AND STABILITY

Store at room temperature (15° to 25 °C). Protect from moisture and humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ratio-LISINOPRIL P is supplied as 5 mg, 10 mg and 20 mg tablets for oral administration.

In addition to the active ingredient lisinopril, each tablet contains the following inactive ingredients: dibasic calcium phosphate dihydrate, lactose monohydrate, povidone, magnesium stearate, pregelatinized starch, yellow iron oxide (10 mg and 20 mg tablets) and red iron oxide (20 mg tablets).

ratio-LISINOPRIL P 5 mg tablets are white, shield-shaped, with rph on one side and L63 on the other. Available in bottles of 100 or 500 tablets

ratio-LISINOPRIL P 10 mg yellow color, shield-shaped, with rph on one side and L62 on the other. Available in bottles of 100 or 500 tablets

ratio-LISINOPRIL P 20 mg peach color, shield-shaped, with rph on one side and L61 on the other. Available in bottles of 100 or 500 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

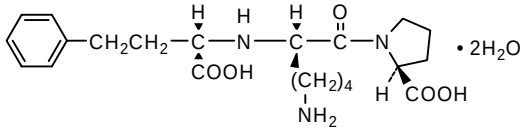
Drug Substance

Proper name: lisinopril

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

Molecular formula and molecular mass: $C_{21}H_{31}N_3O_5 \cdot 2H_2O$, 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

Successful bioequivalence studies were conducted between Prinivil® (Merck Frosst, Canada) and ratio-LISINOPRIL. The results of the bioequivalence studies are summarized in the tables below.

Single dose study under fasting conditions

A Blind, randomized, 2-way crossover, bioequivalence study of ratio-LISINOPRIL 20 mg tablet and Prinivil® (Merck Frosst, Canada) following a 1 x 20 mg tablet dose in healthy male subjects under fasting conditions (n=21, age=18 to 55 years) was conducted and demonstrated that ratio-LISINOPRIL was bioequivalent to Prinivil®.

Lisinopril (1 x 20 mg) From measured data **uncorrected for potency** Least Square Mean Arithmetic Mean (CV %)				
Parameter¶	Test ratio-LISINOPRIL 20 mg Tablets ratiopharm Inc., Canada	Reference lisinopril (Prinivil®)+ Merck Frosst, Canada	% Ratio of Least Square Mean	90% Confidence Interval
$AUC_{0\text{-}72h}$* (ng·h/mL)	1035.10 1084.72 (29.97)	1135.08 1182.13 (28.25)	91.19%	80.86% to 102.85 %
Cmax (ng/mL)	71.48 75.78 (32.30)	78.17 81.83 (30.25)	91.45%	79.55 % to 105.12 %
Tmax§ (h)	6.60 (11.40)	6.69 (9.88)		

+Prinivil® (manufactured by Merck Frosst, Canada) was purchased in Canada.

* Lisinopril $T_{1/2}$ is over 24 hours and therefore truncated was used.

§ arithmetic mean (CV%)

¶Due to the design of the study, meaningful AUC_I and $t_{1/2}$ parameters could not calculated.

DETAILED PHARMACOLOGY

MECHANISM OF ACTION

Study	Species/strain	No. of Animals/ Group	Route	Dose	Results
In vitro ACE inhibitory activity*	Hog plasma		*In vitro*		IC_{50} = 1.7 ± 0.5 nM
Augmentation of contractile response to bradykinin	Guinea pig ileum	7 segments	*In vitro*		AC_{50} = 1.6 nM
In vivo 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.
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 min.
In vivo ACE inhibition in anesthetized dogs**	Mongrel	6	I.V.	1-30 µg/kg	ID_{50} = 6.5 µg/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 AI challenge.

Study	Species/strain	No. of Animals/ Group	Route	Dose	Results
Effects on Blood Pressure					
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.
Antihypertensive activity in rats on a sodium-deficient diet (single doses)	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 hydro-chlorothiazide	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 0.312-5mg/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.

TOXICOLOGY

A. Acute Toxicity of Lisinopril

1. LD_{50} Values:

Species	Sex	Route	LD_{50} (g/kg)
Mouse	Male	Oral	>20
Mouse	Female	Oral	>20
Rat	Male	Oral	>20
Rat	Female	Oral	>20
Dog	Male	Oral	> 6
Dog	Female	Oral	> 6
Mouse	Male	Intravenous	>10
Mouse	Female	Intravenous	>10
Rat	Male	Intraperitoneal	>10
Rat	Female	Intraperitoneal	>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.

B. 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 to 10%) were observed in female rats. At 10 to 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 and focal necrosis of the glandular mucosa of the stomach. 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 was 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 post-treatment at 300 mg.

[a] Dosing terminated Week 11, rats killed Week 27.

B. Subacute/Chronic Toxicology (continued)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
Dog	2-Week	3 F + 3 M	Oral	3, 10, 30	At 30 mg, 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%).
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.

B. Subacute/Chronic Toxicology (continued)

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
Dog	3-Month with 1-Month Recovery (high dose)	Control 5 M + 5F 3, 10, 30 mg/kg/day 3 M + 3F 100 mg/kg/day 8 M + 8F Recovery Control 2 M + 2F 100 mg/kg/day 5 M + 5F	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-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.

C. 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 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 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.

D. Fertility and Late Gestation and Lactation with Postnatal Evaluation Studies

Species	No. of Animals/Group	Dose mg/kg/day	Route	Duration of Dosing	Results
Rat	24 F & 24 M	30, 100, 300, 300 with saline	Oral	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	30, 100, 300, 300 with saline	Oral	Day 15 of gestation through Day 21 post-partum	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.

E. 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 :g/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

F. Carcinogenicity Studies

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
Mice Crl:CD-1(ICR)BR	92-Week	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 Crl:CD (SD) BR	105-Week	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 at termination of study was seen (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 Hypertension 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;29:665-70.

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;14:363-8.

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;11:461-7.

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. Curr Therap Res 1985;37:342-51.

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 Cardiovasc Pharmacol 1987;9(Suppl 3):S89-S97.

7. 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 Pharmacol 1988;25:533-8.

8. Dahlöf B, Himmelmann A. The effect of lisinopril on left ventricular morphology and function: Focus on hypertensive cardiac hypertrophy. Rev Comtemp Pharmacother 1993;4(2):123-31.

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

10. Donohoe JF, Kelly J, Laher MS, Doyle GD. Lisinopril in the treatment of hypertensive

patients with renal impairment. Am J Med 1988;85(Suppl 3B):31-4

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):1240-6.

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;343:1115-22.

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

14. Millar JA, Derkx FHM, McLean K, Reid JL. Pharmacodynamics of converting enzyme inhibition: The cardiovascular endocrine and autonomic effects of MK421 (enalapril) and MK-521. Br J Clin Pharmacol 1982;14:347-55.

15. Myers MG, Carruthers SG, Leenen FHH, Haynes RB. Recommendations from the Canadian Hypertension Society Consensus Conference on the Pharmacologic Treatment of Hypertension: Consensus Conference Report. Can Med Assoc J 1989;140:1141-6.

16. 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 R, and co-investigators. A double-blind comparison of lisinopril with captopril in patients with symptomatic congestive heart failure. J Cardiovasc Pharmacol 1987;9(Suppl 3):S82-S88.

17. 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):116-9.

18. Ulm EH, Hichens M, Gomez HJ, Till AE, Hand E, Vassil TC, Biollaz J, Brunner HR, Schelling JL. Enalapril maleate and a lysine analogue (MK-521): Disposition in man. Br J Clin Pharmacol 1982;14:357-62.

19. Product Monograph, Prinivil® (lisinopril), Merck Frosst Canada & Co., Date of Revision: January 9, 2007.

PART III: CONSUMER INFORMATION
ratio-LISINOPRIL P
lisinopril

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

ABOUT THIS MEDICATION

ratio-LISINOPRIL P is available **only on prescription** from your doctor.

What the medication is used for:

- reducing high blood pressure
- treating patients with heart failure, which is a condition where the heart cannot pump adequate amounts of blood to satisfy the needs of the body
- improving survival after heart attack

When blood pressure is high, the workload of the heart and arteries increases so that over time, these organs may not function as they should. As a consequence, this could lead to the damage of the "vital organs": brain - heart - kidneys, resulting in stroke, heart failure, heart attack, blood vessel disease or kidney disease.

What it does:

ratio-LISINOPRIL P is one of a class of medicines known as angiotensin converting enzyme (ACE) inhibitors.

ratio-LISINOPRIL P tablets can lower blood pressure by preventing the effect of angiotensin II - a natural substance in your body that narrows your blood vessels. This narrowing can increase your blood pressure and force your heart to work harder.

Read the following information carefully. **If you need any explanations, or further information, ask your doctor or pharmacist.**

When it should not be used:

Do not take ratio-LISINOPRIL P, if you:

- are allergic to lisinopril or any component of this product (see What the important non-medicinal ingredients are)
- are allergic to angiotensin converting enzyme inhibitors (medication of the same type with the names usually ending with 'pril' such as lisinopril, enalapril, captopril, etc.)
- have a history of angioneurotic edema (symptoms such as swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) relating to previous treatment with an ACE-inhibitors.
- have been diagnosed with hereditary (family history) or idiopathic (unknown origin) angioneurotic edema (please refer to Side Effects and What to do About Them)

What the medicinal ingredient is:

Lisinopril

What the important non-medicinal ingredients are:

Dibasic calcium phosphate dihydrate, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch, yellow iron oxide (10 mg and 20 mg tablets) and red iron oxide (20 mg tablets).

What dosage forms it comes in:

Tablets of 5 mg (white), 10 mg (yellow) and 20 mg (peach) strengths.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

BEFORE you use ratio-LISINOPRIL P talk to your doctor or pharmacist if:

- You have previously taken lisinopril or other medication of the same type - angiotensin-converting enzyme (ACE) inhibitors with the names usually ending with 'pril' such as lisinopril, enalapril, captopril, etc., 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. You should not take ratio-LISINOPRIL P if you have had these types of reactions without a known cause or if you have been diagnosed with hereditary or idiopathic angioedema (symptoms such a swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing).
- **You are pregnant, breast-feeding or thinking of becoming pregnant.** Taking ratio-LISINOPRIL P 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 ratio-LISINOPRIL P, stop the medication and report to your physician as soon as possible. It is possible that ratio-LISINOPRIL P passes into breast milk. You should not breast-feed while taking ratio-LISINOPRIL P.
- You suffer from low blood pressure (you may notice this as faintness or dizziness, especially when standing)
- You are undergoing dialysis
- You have to undergo any dental or other surgery

- You have any of these conditions:
  - diabetes
  - heart or blood vessel disease
  - liver disease
  - kidney disease

You should also inform your doctor if you are vomiting or have severe diarrhea.

INTERACTIONS WITH THIS MEDICATION

Do not take any other medicines unless you have discussed the matter with your physician or pharmacist. Certain medications tend to increase your blood pressure, for example, non-prescription preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems, or may also react badly with ratio-LISINOPRIL P.

Your doctor also needs to know if you are taking any other medication, whether on prescription or otherwise. It is particularly important to inform your physician if you are taking:

- Diuretics or "water pills", such as spironolactone, triamterene or amiloride
- Other medicines to reduce the blood pressure;
- Potassium-containing medicines, potassium supplements, salt substitutes that contain potassium
- Lithium (a drug used to treat a certain kind of depression)
- Pain and arthritis medicines, such as ibuprofen, indomethacin, diclofenac etc.

PROPER USE OF THIS MEDICATION

Usual Dose:

- Take this medicine exactly as your doctor ordered.
- The absorption of this medicine is not affected by food; so it can be taken with or without a meal.
- Try to take your medicine every day at the same time. This way it becomes easy to remember your doses.
- The maximum daily dose for ratio-LISINOPRIL P oral administration is 80 mg.

Keep your regular appointments with your physician, even if you feel well. High blood pressure may not be easily recognized by you, because you may not "feel any symptoms"; but your doctor can measure your blood pressure very easily, and check how the medicine is controlling it.

If your doctor has recommended a particular diet, for instance - less salt - follow the diet carefully. This could help your medicine to better control your blood pressure. Your doctor may also recommend weight loss. Do follow these suggestions.
This medicine does not cure high blood pressure, **but does help control it**. So, it is important to continue taking the tablets regularly to keep your blood pressure down. You may have to take high blood pressure medicine for life.

Overdose:
In case of an overdose, contact your doctor immediately so that medical attention may be given promptly. The most likely symptom would be a feeling of lightheadedness or dizziness due to a sudden or excessive drop in blood pressure.

Missed Dose:
If you miss a dose of this medicine, take it as soon as possible. However, if no more than 6 hours have elapsed since the missed dose, you may take that day's dose of medication and then go back to your regular dosing schedule. **Do not take a double dose.**

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.**

Do not use outdated medicine.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its intended action, any medication, including ratio-LISINOPRIL P, 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:

- Symptoms of angioedema, such as: sudden difficulty in breathing or swallowing, swelling of face, eyes, lips, tongue and/or throat, hands or feet. You should be aware that 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

Stop taking the medication and contact your doctor or pharmacist at once. You may require immediate care. If condition worsens, seek medical attention.

If any fainting occurs, stop taking the medicine. If dizzy, avoid driving or any activity/job requiring alertness. Use extra care during exercise or hot weather.

- 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
- Dry cough, sore throat
- Unusual tiredness and/or weakness
- Headache
- Less or no urine being produced

IF YOU NOTICE ANY OF THE ABOVE OR HAVE OTHER SIDE EFFECTS, CONTACT YOUR PHYSICIAN OR PHARMACIST. IF THE CONDITION PERSISTS OR WORSENS, SEEK MEDICAL ATTENTION.

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	√		
	Lasting Cough		√	
	Chest pain		√	
	Dyspnea (shortness of breath)		√	
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			√

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

HOW TO STORE IT

Store at room temperature between 15 and 25°C in tightly closed container, away from heat and direct light and out of damp places, such as a bathroom or kitchen. Protect from moisture and humidity.

Keep all medicines out of 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 obtained by contacting the sponsor, ratiopharm inc., at: 1-800-337-2584

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