

PRODUCT MONOGRAPH


PRINIVIL®

(lisinopril tablets, Merck Frosst Std.)

Tablets 2.5, 5, 10 and 20 mg

PHARMACOLOGICAL CLASSIFICATION

ANGIOTENSIN CONVERTING ENZYME INHIBITOR

MERCK FROSST CANADA LTD.
Kirkland, Quebec, Canada

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Angiotensin Converting Enzyme Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

PRINIVIL[®] (lisinopril tablets, Merck Frosst Std.) is an ACE inhibitor which is used in the treatment of hypertension, congestive heart failure and following myocardial infarction in haemodynamically 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 PRINIVIL[®] and a thiazide diuretic there was essentially no change in serum potassium (see PRECAUTIONS).

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

While the mechanism through which PRINIVIL[®] lowers blood pressure is believed

to be primarily the suppression of the renin-angiotensin-aldosterone system, PRINIVIL[®] also lowers blood pressure in patients with low-renin hypertension.

Pharmacodynamics

Administration of PRINIVIL[®] to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of PRINIVIL[®] 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 haemodynamic 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 PRINIVIL[®], 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 PRINIVIL[®] on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

When PRINIVIL[®] 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 PRINIVIL[®] 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 PRINIVIL[®], 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.

INDICATIONS AND CLINICAL USE

Hypertension

PRINIVIL[®] (lisinopril tablets, Merck Frosst Std.) 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. PRINIVIL[®] has been used concomitantly with beta-blockers and calcium antagonists, but the data on such use are limited.

PRINIVIL[®] 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. PRINIVIL[®] 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

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

Treatment Following Acute Myocardial Infarction

PRINIVIL[®] is indicated in the treatment of haemodynamically 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 PRINIVIL[®] should be reassessed after six weeks. If there is no

evidence of symptomatic or asymptomatic left ventricular dysfunction, treatment with PRINIVIL® can be stopped.

PRINIVIL® 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 PRECAUTIONS, Hypotension Following Acute Myocardial Infarction, Renal Impairment).

General

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death to the developing fetus. When pregnancy is detected, PRINIVIL® should be discontinued as soon as possible (see WARNINGS; Use in Pregnancy, and INFORMATION FOR PATIENTS).

In using PRINIVIL®, attention should be given to the risk of angioedema (see WARNINGS).

CONTRAINDICATIONS

PRINIVIL® (lisinopril tablets, Merck Frosst Std.) is contraindicated in patients who:

- are hypersensitive to any component of this product;
- have a history of angioneurotic edema relating to previous treatment with an angiotensin-converting enzyme inhibitor;
- have hereditary or idiopathic angioedema.

WARNINGS

Angioedema

Angioedema has been reported in patients treated with PRINIVIL® (lisinopril tablets, Merck Frosst Std.). This may occur at any time during treatment. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema occurs, PRINIVIL® 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 PRINIVIL[®], 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 PRINIVIL[®] and/or reduced concomitant diuretic therapy should be considered.

If hypotension occurs during treatment following acute myocardial infarction, consideration should be given to PRINIVIL[®] 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 PRINIVIL[®]. 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. Several dozen cases have been reported in the world literature. When pregnancy is detected, PRINIVIL® should be discontinued as soon as possible.

In rare cases (probably less than once in every thousand pregnancies) in which no alternative to ACE inhibitor therapy will be found, the mothers should be apprised of the potential hazards to their fetuses. Serial ultrasound examinations should be performed to assess fetal development and well-being and the volume of amniotic fluid.

If oligohydramnios is observed, PRINIVIL® should be discontinued unless it is considered life-saving for the mother. A non-stress test (NST), and/or a biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. If concerns regarding fetal well-being still persist, a contraction stress testing (CST) should be considered. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

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, experience with those procedures has been limited.

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.

Human Data: It is not known whether exposure limited to the first trimester of pregnancy can adversely affect fetal outcome. 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; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

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.

PRECAUTIONS

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

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 $\mu\text{mol/L}$ and/or proteinuria exceeding 500 mg/24 hour. If renal dysfunction develops during treatment with PRINIVIL[®] (serum creatinine concentration exceeding 265 $\mu\text{mol/L}$ or a doubling from the pre-treatment value), then the physician should consider withdrawal of PRINIVIL[®].

Use of PRINIVIL[®] 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 haemodynamic 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 PRINIVIL[®] 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.

PRINIVIL[®] 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 PRINIVIL[®] 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 PRINIVIL[®] should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. PRINIVIL[®] 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 PRINIVIL[®] has been reported.

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

Use in Nursing Mothers

Exercise caution when giving PRINIVIL[®] to lactating women. Milk of lactating rats contains radioactivity following administration of ¹⁴C lisinopril. It is not known whether PRINIVIL[®] is secreted in human breast milk.

Use in the Elderly

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of PRINIVIL[®]. 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.

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, 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 PRINIVIL[®] 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 non-steroidal 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 PRINIVIL[®].

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.

INFORMATION FOR PATIENTS

Angioedema

Angioedema, including laryngeal edema, may occur especially following the first dose of lisinopril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension

Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.

Neutropenia

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

Impaired liver function

Patients should be advised to return to the physician if he/she experiences any symptoms possibly related to liver dysfunction. This would include "viral-like symptoms" in the first weeks to months of therapy (such as fever, malaise, muscle pain, rash or adenopathy which are possible indicators of hypersensitivity reactions), or if abdominal pain, nausea or vomiting, loss of appetite, jaundice, itching or any other unexplained symptoms occur during therapy.

Hyperkalemia

Patients should be told not to use salt substitutes containing potassium without

consulting their physician.

Pregnancy

Patients should be advised to report promptly to their physician if they become pregnant, since the use of PRINIVIL[®] during pregnancy can cause injury and even death of the developing fetus.

NOTE

As with many other drugs, certain advice to patients being treated with PRINIVIL[®] is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

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 PRINIVIL® (lisinopril tablets, Merck Frosst Std.) in controlled clinical trials, comparative incidence data are listed in the table below.

**INCIDENCE OF ADVERSE REACTIONS
OCCURRING IN PATIENTS TREATED WITH PRINIVIL®
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

	HYPERTENSION (2633 PATIENTS) %	CONGESTIVE HEART FAILURE (636 PATIENTS) %
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 PRINIVIL® (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 PRINIVIL® should be discontinued and appropriate therapy instituted immediately (see WARNINGS, 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).

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, Hypotension)
- Tachycardia

Dermatologic

- Alopecia
- Diaphoresis
- Pruritis
- Urticaria

Severe skin disorders such as:

- 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 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 PRINIVIL[®] alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see 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 PRINIVIL[®] 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, Neutropenia/Agranulocytosis).

Hepatic

Elevations of liver enzymes and/or serum bilirubin have occurred (see 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%).

SYMPTOMS AND TREATMENT OF 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 PRECAUTIONS, Anaphylactoid Reactions during Membrane Exposure).

DOSAGE AND ADMINISTRATION

Since absorption of PRINIVIL[®] tablets (lisinopril tablets, Merck Frosst Std.) is not affected by food, the tablets may be administered before, during or after meals. PRINIVIL[®] should be administered in a single daily dose. PRINIVIL[®] should be taken at the same time each day.

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 PRINIVIL[®] 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 PRINIVIL[®].

Diuretic Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of PRINIVIL[®]. The diuretic should be discontinued, if possible, for two to three days before beginning therapy with PRINIVIL[®] to reduce the likelihood of hypotension (see WARNINGS). The dosage of PRINIVIL[®] should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with PRINIVIL[®] 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, Hypotension and PRECAUTIONS, 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
$\leq 70 \geq 30$ mL/min ($\leq 1.17 \geq 0.5$ mL/s)	5.0 - 10.0 mg/day
$\leq 30 \geq 10$ mL/min ($\leq 0.5 \geq 0.17$ 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 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 PRINIVIL[®]. 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 PRINIVIL[®]. 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

PRINIVIL[®] 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 PRINIVIL[®], because severe hypotension and, more rarely, consequent renal failure have been reported (see WARNINGS, Hypotension and PRECAUTIONS, 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 haemodynamically 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 PRINIVIL[®] is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily thereafter.

Patient 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 PRINIVIL[®] must not be initiated in patients who are at risk of serious hemodynamic deterioration (see 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), PRINIVIL® should be withdrawn.

Renal function should be assessed before and during therapy with PRINIVIL® (see PRECAUTIONS, Renal Impairment).

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

PRINIVIL® is compatible with intravenous or transdermal glyceryl trinitrate.

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

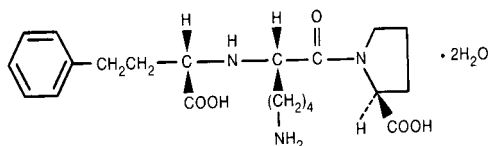
Proper name: Lisinopril

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

Molecular formula: C₂₁H₃₁N₃O₅·2H₂O

Molecular weight: 441.53

Structural formula:



Description:

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

II. COMPOSITION

PRINIVIL[®] is supplied as 2.5 mg, 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: calcium phosphate, corn starch, magnesium stearate, and mannitol. The 10 mg and 20 mg tablets also contain iron oxide.

III. STABILITY AND STORAGE RECOMMENDATIONS

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

AVAILABILITY OF DOSAGE FORMS

Tablets PRINIVIL[®], 2.5 mg, are white, round flat-faced beveled-edged compressed tablets, with code MSD on one side and number 15 on the other side. Available in bottles of 30 and 100 tablets and in blister packages of 30 tablets.

Tablets PRINIVIL[®], 5 mg, are white, shield-shaped, scored, compressed tablets, with code MSD 19 on one side and PRINIVIL on the other. Available in bottles of 100 tablets and in blister packages of 30 tablets.

Tablets PRINIVIL[®], 10 mg, are yellow, shield-shaped, compressed tablets, with code MSD 106 on one side and PRINIVIL on the other. Available in bottles of 100 tablets and in blister packages of 30 tablets.

Tablets PRINIVIL[®], 20 mg, are peach, shield-shaped, compressed tablets, with code MSD 207 on one side and PRINIVIL on the other. Available in bottles of 100 tablets and in blister packages of 30 tablets.

INFORMATION FOR THE PATIENT

PRINIVIL® Tablets

PRINIVIL® is the brandname of Merck Frosst Canada Ltd. 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. They are usually prescribed to reduce **high blood pressure**.

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.

PRINIVIL® may also be used to treat patients with **heart failure**. This is a condition where the heart cannot pump adequate amounts of blood to satisfy the needs of the body.

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.

Keep all medicines out of the reach of children.

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

BEFORE TAKING THIS MEDICINE

This medicine may not be suitable for certain people. So, tell your physician if you think **any** of the following applies to you:

- . 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 PRINIVIL[®] if you have had these types of reactions without a known cause or if you have been diagnosed with hereditary or idiopathic angioedema.

- . **You are pregnant or intend to become pregnant.** This medicine should **not be used during pregnancy**, because of possible risks to the fetus.

- . You are breast-feeding or intend to breast-feed.

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

Your physician 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"; any other medicines to reduce blood pressure; potassium-containing medicines, potassium supplements, salt substitutes that contain potassium, lithium (a drug used to treat a certain kind of depression) or certain pain and arthritis medicines.

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

This medicine is not recommended for children.

PROPER USE OF THIS MEDICINE

- . Take this medicine exactly as your physician 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.

- . 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.

- . 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.

- . 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.

- . If your physician has recommended a particular diet, for instance - less salt - follow the diet carefully. Your physician may also recommend weight loss. Do follow these suggestions.

- . This medicine does not cure high blood pressure, nor congestive heart failure, **but does help control these conditions.** So, it is important to continue taking the tablets regularly. You may have to take high blood pressure

medicine for life.

- . 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 physician can measure very easily and check how the medicine is helping to control it.
- . **Do not take any other medicines** unless you have discussed the matter with your physician. Certain medications tend to increase your pressure, for example, non-prescription preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems. Other medicines may also react badly with PRINIVIL®.
- . If you have to undergo any dental or other surgery, inform the dentist or the physician in charge that you are taking this medicine.

SIDE EFFECTS OF THIS MEDICINE - AND WHAT YOU SHOULD DO

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.

- . 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 PHYSICIAN OR PHARMACIST AT ONCE. YOU MAY REQUIRE IMMEDIATE CARE. IF CONDITION WORSENS, SEEK MEDICAL ATTENTION.

- . 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
- . 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
- . 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.

INGREDIENTS

Active ingredient: Each tablet of PRINIVIL® contains lisinopril. There are four different strengths: 2.5 mg (white), 5 mg (white), 10 mg (yellow) and 20 mg (peach).

Non-medicinal ingredients: calcium phosphate, corn starch, magnesium stearate, and mannitol. The 10 mg and 20 mg also contain iron oxides.

PHARMACOLOGY

Study	Species/strain	No. of Animals/Group	Route	Dose	Results
MECHANISM OF ACTION					
<i>In vitro</i> ACE inhibitory activity*	Hog plasma		<i>In vitro</i>		IC ₅₀ = 1.7 ± 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 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 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 (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 hydrochlorothiazide	SH rats	3 - 6	P.O.	1.25 mg/kg HCTZ = 50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3-5 days. 2 hours after drug administration, lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ, the average mean arterial pressure was reduced from 202 to 132 mmHg.
Antihypertensive activity in spontaneously hypertensive rats (single doses)	SH rats	3 - 9	P.O. & I.V.	0.1-20 mg/kg	Slight fall in blood pressure at 0.312-5 mg/kg P.O. Pronounced fall at 20 mg/kg P.O. and 0.1 mg/kg I.V. with statistically significant reductions being observed for the majority of time points between 1/2 - 18 hours.

TOXICOLOGY

A. Acute Toxicity of Lisinopril

1. LD₅₀ 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 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 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-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 Weeks	6 F	Oral	15 (1, 6 & 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6, and 13 doses.

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 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.

E. 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

F. 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 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.

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