PRODUCT MONOGRAPH

[Pr]LISINOPRIL

(lisinopril tablets, USP)

Tablets 5, 10 and 20 mg

Angiotensin Converting Enzyme Inhibitor

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Date of Revision:
April 19, 2011

Submission Control No: 145664

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(lisinopril tablets, USP)

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THERAPEUTIC CLASSIFICATION

Angiotensin Converting Enzyme Inhibitor

ACTIONS AND CLINICAL PHARMACOLOGY

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

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

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

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

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

smaller 24 hours after dosing than it was 6 hours after dosing. On occasion, achievement of optimal blood pressure reduction may require 2 to 4 weeks of therapy.

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

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

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

In the Assessment of Treatment with Lisinopril and Survival Study (ATLAS) higher doses of lisinopril up to 35 mg once daily reduced the risk of the combined outcome of mortality and hospitalization in patients with chronic congestive heart failure. The ATLAS study was an international, multicenter, double-blind, parallel group clinical trial which evaluated the effects of low doses, 2.5 mg-5.0 mg, versus high doses, 32.5 mg-35.0 mg lisinopril on mortality and morbidity in patients with chronic congestive heart failure. A total of 1596 patients were randomized into the low dose and 1568 into the high dose groups. Patients entered into the ATLAS study were NYHA Class II, III, or IV, were treated with diuretics for at least 60 days prior to entry into the study, and had a left ventricular ejection fraction (LVEF) $\leq$ 30 %. Class II patients were eligible only if they were hospitalized or received emergency room treatment in the previous six months. Prior treatment with ACE inhibitors and digoxin was permitted, and patients were permitted routine therapies, other than ACE inhibitors, for the duration of the study. The median follow-up period was 46 months. The protocol excluded patients with recent cardiac surgery, unstable coronary artery disease, unstable ventricular arrhythmias, unstable CHF, or a non-CHF disorder that may have limited survival during the course of the trial. Overall, 77 % of patients were NYHA class III; 89 % had previous ACE inhibitor treatment. For the principal secondary endpoint, all-cause mortality and all-cause hospitalization, high dose lisinopril was associated with an 11.6 % ($p=0.002$) risk reduction over low dose (2.5 and 5 mg). High dose lisinopril was also associated with an 8.4 % risk reduction in all-cause mortality and cardiovascular hospitalizations ($p=0.036$). The total number of hospitalizations per patient for heart failure was reduced by 23.2 % ($p=0.002$).

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

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

Lisinopril can be removed by dialysis.

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

INDICATIONS AND CLINICAL USE

Hypertension

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

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

LISINOPRIL can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Heart Failure

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

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

Treatment Following Acute Myocardial Infarction

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

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

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

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

CONTRAINDICATIONS

LISINOPRIL (lisinopril) is contraindicated in patients who:

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

WARNINGS

Serious Warnings and Precautions

When used in pregnancy, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, lisinopril should be discontinued as soon as possible (see WARNINGS - Use in Pregnancy, and Information for the Patients).

Angioedema

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

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension

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

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

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with lisinopril. 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, lisinopril should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function, associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development.

Prematurity, and patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have also been reported following exposure in the first trimester of pregnancy.

Infants with a history of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed towards support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

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

Animal Data

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

Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man.
Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at an oral dose of lisinopril of 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). A single intravenous dose of 15 mg/kg of lisinopril administered to pregnant rabbits on gestation days 16, 21 or 26 resulted in 88 % to 100 % fetal death.

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

Use in Nursing Mothers

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

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

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

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

Use of lisinopril should include appropriate assessment of renal function.

Hypotension Following Acute Myocardial Infarction

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

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

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

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

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with lisinopril. (See PRECAUTIONS – Drug Interactions).

Anaphylactoid Reactions During Membrane Exposure

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

Anaphylactoid Reactions During Desensitization

There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitizing treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia

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

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

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

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

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 Children

Safety and effectiveness in children have not been established.

Occupation Hazards

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

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).

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

Potassium Supplements, potassium-sparing agents or potassium-containing salt substitutes

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

Agents Causing Renin Release

The antihypertensive effect of lisinopril is augmented by antihypertensive agents that cause renin release (e.g. diuretics).

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

NSAIDS

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

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered lisinopril.

Lithium Salts

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

Gold

Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

Antidiabetics

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

Information for the Patients

Serious Warning and Precautions

LISINOPRIL should not be used during pregnancy. Patients should be advised to stop the medication and contact their physician as soon as possible if they discover that they are pregnant while taking LISINOPRIL.

Angioedema

Angioedema, including laryngeal edema and, 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 light headedness 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.

You are pregnant, breast-feeding or thinking of becoming pregnant?

Taking LISINOPRIL during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you become pregnant while taking LISINOPRIL, stop the medication and report to your doctor as soon as possible. It is possible that LISINOPRIL passes into breast milk. You should not breast-feed while taking LISINOPRIL.

NOTE: As with many other drugs, certain advice to patients being treated with LISINOPRIL 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, excluding the ATLAS CHF study patients (see ACTION and CLINICAL PHARMACOLOGY), the most frequent clinical adverse reactions were: dizziness (4.4 %), headache (5.6 %), asthenia/fatigue (2.7 %), diarrhea (1.8 %) and cough (3.0 %), all of which were more frequent than in placebo-treated patients. Discontinuation of therapy was required in 5.9 % of patients.

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

Adverse Events in Controlled Clinical Trials

Incidence of Adverse Reactions Occurring in Patients Treated with lisinopril In Controlled Clinical Trials.

		Hypertension n=2 633 (%)	**Congestive Heart Failure n=636** (%)
Cardiovascular	Hypotension	0.8	5.2
	orthostatic effects	0.9	1.3
	chest pain	1.1	7.4
	angina	0.3	3.8
	edema	0.6	2.5
	palpitation	0.8	1.9
	rhythm disturbances	0.5	0.6
Gastrointestinal	Diarrhea	1.8	6.1
	Nausea	1.9	4.9
	Vomiting	1.1	2.4
	Dyspepsia	0.5	1.9
	Anorexia	0.4	1.4
	Constipation	0.2	0.8
	flatulence	0.3	0.5
Nervous System	Dizziness	4.4	14.2
	Headache	5.6	4.6
	Paresthesia	0.5	2.8
	Depression	0.7	1.1
	Somnolence	0.8	0.6
	Insomnia	0.3	2.4
	vertigo	0.2	0.2
Respiratory	Cough	3.0	6.4
	Dyspnea	0.4	7.4
	orthopnea	0.1	0.9
Dermatologic	Rash	1.0	5.0
	pruritus	0.5	1.4
Musculoskeletal	muscle cramps	0.5	2.2
	back pain	0.5	1.7
	leg pain	0.1	1.3
	shoulder pain	0.2	0.8

		Hypertension n=2 633 (%)	Congestive Heart Failure n=636 (%)
Other	asthenia/fatigue	2.7	7.1
	blurred vision	0.3	1.1
	fever	0.3	1.1
	flushing	0.3	0.3
	gout	0.2	1.7
	decreased libido	0.2	0.2
	malaise	0.3	1.1

Angioedema

Angioedema has been reported in patients receiving lisinopril (0.1 %). In very rare cases, intestinal angioedema has been reported (see WARNINGS - Angioedema).

Hypotension

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

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

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

Treatment Following Acute Myocardial Infarction

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

Event	Control n=4729	Lisinopril n=4713	Lisinopril + GTN n=4722	GTN Alone n=4731
Persistent Hypertension	3.6	8.8	9.3	3.9
Shock	2.5	2.8	2.2	1.9
Renal Dysfunction	1.1	2.4	2.4	1.1
Stroke	0.6	0.6	0.9	0.8
Re-Infarction	2.2	2.2	2.2	1.9
Hemorrhagic Events	1.2	1.3	1.1	0.9
Post-Infarction Angina	13.2	13.9	12.3	11.8
Ventricular Fibrillation	3.1	2.5	2.4	2.2
Sustained Ventricular Tachycardia	2.5	2.1	1.8	2.3
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

Laboratory Test Findings

Serum Electrolytes

Hyperkalemia (see PRECAUTIONS - Hyperkalemia).

Creatinine, Blood Urea Nitrogen

Increases in blood urea nitrogen and serum creatinine, usually reversible upon discontinuation of therapy, were observed in 1.1 and 1.6 % of patients respectively with essential hypertension treated with lisinopril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see PRECAUTIONS – Renal Impairment). In patients with congestive heart failure on 2.5 to 20 mg lisinopril and concomitant diuretic therapy, reversible increases in blood urea nitrogen (14.5 %) and serum creatinine (11.2 %) were observed in approximately 12.0 % of patients. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

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

withdrawal. Therapy discontinuation rates due to increased serum creatinine for high versus low dose were 0.3 % versus 0.4 %, respectively.

Hematology

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

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

Hepatic

Elevations of liver enzymes and/or serum bilirubin have occurred (see PRECAUTIONS - Patients with Impaired Liver Function).

Discontinuations

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

Post-Marketing Experience

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

Blood and lymphatic system disorders
Very rare: bone marrow depression, anemia thrombocytopenia, leucopenia, agranulocytosis, hemolytic anemia (see WARNINGS – Neutropenia/Agranulocytosis).

Endocrine disorders
Rare: inappropriate antidiuretic hormone secretion

Metabolism and nutrition disorders
Uncommon: hyperkalemia (see PRECAUTIONS – Hyperkalemia).
Rare: hyponatremia.
Very rare: hypoglycaemia (see PRECAUTIONS – Diabetic Patients).

Nervous system and psychiatric disorders

Common: dizziness, headache.

Uncommon: mood alterations (including depressive symptoms), paraesthesia**,** vertigo, taste disturbance, sleep disturbances.

Rare: mental confusions, olfactory disturbance.

Cardiac and vascular disorders

Common: orthostatic effects (including hypotension) (see WARNINGS – Hypotension), syncope (frequency refers to congestive heart failure patient population, frequency in hypertensive patient population is "uncommon").

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

Respiratory, thoracic and mediastinal disorders:

Common: cough.

Uncommon: rhinitis.

Very rare: bronchospasm, sinusitis.

Gastrointestinal disorders

Common: diarrhoea, vomiting.

Uncommon: nausea, abdominal pain and indigestion.

Rare: dry mouth.

Very rare: pancreatitis, intestinal angioedema (See WARNINGS – Angioedema and ADVERSE EVENTS – Angioedema).

Hepato-biliary disorders

Very rare: hepatitis – either hepatocellular or cholestatic, jaundice, hepatic failure. Very rarely it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving lisinopril who develop jaundice or marketed elevation of hepatic enzymes should discontinue lisinopril and receive appropriate medical follow-up (See PRECAUTIONS – Patients with Impaired Liver Function).

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritis, hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis, and/or larynx (See WARNINGS – Angioedema).

Rare: urticaria, alopecia, psoriasis.

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

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

Renal and urinary disorders
Common: renal dysfunction.
Rare: uremia, acute renal failure.
Very rare: oliguria/anuria (see PRECAUTIONS – Renal Impairment).

Reproductive system and breast disorders
Uncommon: impotence.

General disorders and administration site conditions
Uncommon: fatigue, asthenia.

Investigations
Uncommon: increases in blood urea, increases in serum creatinine (see PRECAUTIONS – Renal Impairment), increases in liver enzymes (see PRECAUTIONS – Patients with Impaired Liver Function).
Rare: decreases in hemoglobin, decreases in hematocrit, increases in serum bilirubin (see PRECAUTIONS – Patients with Impaired Liver Function).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

Essential Hypertension

In patients with essential hypertension, not on diuretic therapy, the usual recommended starting dose is 10 mg once a day. The usual dosage range is 10 to 40 mg per day, administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. The maximum dose used in long-term controlled clinical trials was 80 mg/day. If blood pressure is not controlled with LISINOPRIL alone, a low dose of diuretic may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of diuretic, it may be possible to reduce the dose of LISINOPRIL.

Diuretic Treated Patients

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

If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS - 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 mg/day
mL/s	mL/min	
0.50-1.17	31-70	5.0-10.0
0.17-0.50	10-30	2.5-5.0
<0.17 (including patients on dialysis)	<10 (including patients on dialysis)	2.5*

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

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

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g.:polyacrylonitrile [PAN]and during low-density lipoproteins (LDL) apheresis with dextran suphate) 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 LISINOPRIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Renovascular Hypertension

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

Congestive Heart Failure

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

- by increments of no greater than 10 mg,

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

Treatment Following Acute Myocardial Infarction

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

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

Patients with a low systolic blood pressure (between 100 and 120 mmHg) when treatment is started or during the first 3 days after the infarct should be given a lower dose - 2.5 mg orally. Treatment with LISINOPRIL must not be initiated in patients who are at risk of serious hemodynamic deterioration (see 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 1 hour), LISINOPRIL should be withdrawn.

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

LISINOPRIL is compatible with intravenous or transdermal glyceryl trinitrate.

PHARMACEUTICAL INFORMATION

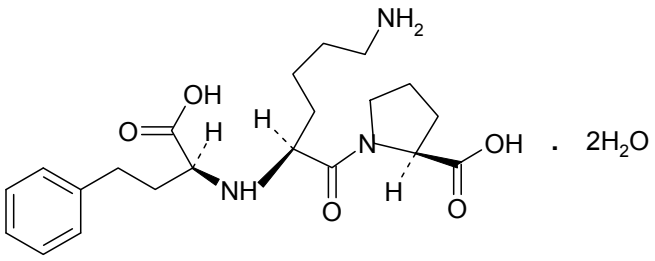
Drug Substance

Trade Name: LISINOPRIL

Proper name: lisinopril

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

Structural Formula:



Molecular Formula: $C_{21}H_{31}N_3O_5 \bullet 2\ H_2O$

Molecular Weight: 441.53

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.

Composition

LISINOPRIL is supplied as 5 mg, 10 mg and 20 mg tablets for oral administration.
Tablets contain 5 mg, 10 mg and 20 mg lisinopril (on anhydrous basis) and each tablet contains the following non-medicinal ingredients: dibasic calcium phosphate anhydrous, hydroxypropyl methylcellulose, iron oxides, mannitol, magnesium stearate, polyethylene glycol, pregelatinized starch and titanium dioxide.

Storage Conditions

Store between 15 ^oC and 30 ^oC.

AVALABILITY OF DOSAGE FORMS

Availability of Dosage Forms

LISINOPRIL 5 mg tablets are pink, oval, biconvex, coated and are debossed with "LS" over "5" on unscored side and nothing on scored side. Available in HDPE bottles of 100, 500 tablets and blister pack of 30 tablets.

LISINOPRIL 10 mg tablets are pink, oval, biconvex, coated and are debossed with "LS" over "10" on one side and nothing on the other side. Available in HDPE bottles of 100, 500 tablets, and blister pack of 30 tablets.

LISINOPRIL 20 mg tablets are deep pink, oval, biconvex, coated and are debossed with "LS" over "20" on one side and nothing on other side. Available in HDPE bottles of 100, 500 tablets, and blister pack of 30 tablets.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single-dose, two-way crossover, blinded comparative bioavailability study of LISINOPRIL 20 mg Tablets, manufactured by Sorres Pharma Inc. was performed versus ZESTRIL®, manufactured by AstraZeneca Canada Inc. and administered as 1 x 20 mg Tablet in healthy male volunteers (n=27) in the Fasting State. Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Lisinopril (1 x 20 mg tablet) From measured data uncorrected for potency Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval (90 %)**
$AUC_{(0\text{-}72h)}$** (ng·h/mL)	1266.89 1314.48 (26.30)	1225.60 1295.18 (34.94)	103.65	90.36 – 118.90
AUC_I (ng·h/mL)	1293.00 1339.97 (25.88)	1257.71 1324.23 (33.91)	103.08	90.25 – 117.73
C_{max} (ng/mL)	89.82 93.95 (29.33)	86.93 92.95 (35.16)	103.62	89.19 – 120.38
T_{max}§ (h)	7.50 (4.00 – 9.00)	7.50 (4.00 – 10.00)		
$T_{½}$€ (h)	12.29 (32.82)	12.08 (41.29)		

* LISINOPRIL 20 mg Tablets (Sorres Pharma Inc..)
† Zestril® (lisinopril), 20 mg Tablets (AstraZeneca, Canada Inc.) were purchased in Canada.
§ Expressed as the median (range) only
€ Expressed as the arithmetic mean (CV %) only
** The parameter AUC $_{(0\text{-}72h)}$ is stated in the table as opposed to AUC_T, due to the long elimination half-life of lisinopril.

PHARMACOLOGY

Mechanism of Action

Study	Species/Strain	Number of Animals/ Group	Route	Dose	Results
in vitro ACE inhibitory activity*	hog plasma		*in vitro*		IC_{50} = ±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 mins.
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 A1 challenge.

Effects on Blood Pressure

Study	Species/Strain	Number of Animals/ Group	Route	Dose	Results
antihypertensive activity in renal hypertensive dogs (single doses)	Mongrel	3	p.o.	0.3 mg/kg with and without 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	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 daily for 4 days.
antihypertensive activity in 2 kidney Grollman hypertensive rats (single doses)	Male Sprague/Dawley	6 - 7	p.o.	1 & 3 mg/kg	At 2 hours: approx. 6 % reduction in mean systolic pressure vs pretreatment with the antihypertensive effect lasting up to 24 hours.
antihypertensive activity in spontaneously hypertensive rats with and without hydrochlorothiazide	SH rats	3 - 6	p.o.	1.25 mg/kg HCTZ = 50 mg/kg daily for 3 days	Enhancement of hypotensive activity over 3-5 days. 2 hours after drug administration, lisinopril alone reduced the average mean arterial pressure from 198 to 161 mmHg. In combination with HCTZ the average mean arterial pressure was reduced from 202 to 132 mmHg.
antihypertensive activity in spontaneously hypertensive rats (single doses)	SH rats	3 – 9	p.o. & i.v.	0.1 – 20 mg/kg	Slight fall in blood pressure at 0.312-5 mg/kg p.o. Pronounced fall at 20 mg/kg p.o. and 0.1 mg/kg i.v. with statistically significant reductions being observed for the majority of time points between 1/2-18 hours.

TOXICOLOGY

Acute Toxicity of Lisinopril

LD_{50} Values

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

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

Subacute/Chronic Toxicology

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

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

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, slight mineralization of the papilla muscle of the heart was seen in 1 of 6 dogs.
Dog	3-month with 1-month Interim	5 F + 5 M	Oral	3,10,30	At 10 mg, hemoglobin concentration, hematocrit, and erythrocyte count decreased in 2 dogs. Marked increases in serum urea nitrogen and creatinine were observed in 2 of 10 dogs. One of these dogs had marked renal tubular degeneration and ulcers of the tongue, gums, and gastric pyloric mucosa related to uremia. At 30 mg there was an increase in serum urea nitrogen (average up to 2-fold) and a decrease in serum sodium (down to 4 mEq/L) and serum chloride (down to 3 mEq/L). At 10 and 30 mg, average cardiac weight decreased (13 to 15 %).
Dog	1-Year with 6-Month Interim	5 F + 5 M	Oral	3,5,15	At 15 mg, increases were observed in serum urea nitrogen (less than 2-fold). Decreases in serum sodium (average down to 2 mEq/L) and increases in serum potassium (average up to 0.5 mEq/L) occurred at all doses.
Dog	18-Day	3 F + 3 M	Oral	60/90 with and without saline	Saline supplementation prevented increases in serum urea nitrogen in dogs given 60 mg for 8 days followed by 90 mg for 8 or 9 days.
Dog	7-Day	4 F + 4 M	i.v.	60,90	Decreases in blood pressure and increases in serum urea nitrogen occurred in dogs given 60 or 90 mg/kg/day. Supplementation with physiologic saline (25 mL/kg one hour prior to dosing and 4 hours after dosing) prevented these changes. Increased serum potassium (average up to 0.6 mEq/L) and decreased serum chloride (average down to 0.4 mEq/L) values were seen in both supplemented and unsupplemented animals.

Subacute/Chronic Toxicology (continued)

Species	Duration	No. Of Animals/ Group	Route	Dose mg/kg/day	Effects
Dog	1-Month	2 F + 2 M	Oral	3,30,300 and 1000	At 30 mg or greater, BUN increased and specific gravity of the urine decreased. Hyperplasia of renal epithelial cells was observed and deaths occurred. Dogs that died had dilation of distal renal tubules and fatty degeneration epithelium. No drug-related effects were observed at 3 mg.
Dog	3-month with 1-month Recovery (high dose)	Control 5 M + 5 F 3, 10 & 30 mg/kg/day 3 M + 3 F 100 mg/kg/day 8 M + 8 F Recovery Control 2 M + 2 F 100 mg/kg/day 5 M + 5 F	Oral	3,10,30 and 100	Eight of 16 dogs given 100 mg died or were killed because of poor physical condition. One of 6 dogs given 30 mg was killed because of poor physical condition. At 10 mg or greater increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible as only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.
Rabbit	2-weeks	6 F	Oral	15 (1,6 & 13 doses) with and without saline	Renal tubular basophilia and renal tubular dilation (considered sequela to necrosis) were seen after 6 and 13 doses in unsupplemented rabbits. Two supplemented rabbits (6 doses) also had the same renal lesion. One rabbit drank very little saline and had increases in BUN, creatinine, and potassium. Increases in these parameters were seen in unsupplemented animals after 1, 6, and 13 doses.

Teratology Studies

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

Fertility and Late Gestation and Lactation with Postnatal Evaluation Studies

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

Genotoxicity Studies

Study	Test System	Dose	Results
Mutagenesis			
Microbial mutagen with and without metabolic activation	*Salmonella typhimurium* TA 1535, TA1537, TA98, TA100	up to 2000 µg/plate	Negative for mutagenic potential.
	Escherichia coli WP2, WP2 uvrA	up to 10 mg/plate	
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.
DAN Damage			
In vitro alkaline elution	Rat Hepatocyte	up to 30 mM (13.25 mg/mL)	Negative for induction of DNA single strand breaks.
Chromosomal Evaluation			
In vitro chromosomal aberration assay with and without metabolic activation	Chinese Hamster Ovary	up to 30 mM (13.25 mg/mL)	Negative for induction of chromosomal aberration.
In vivo chromosomal aberration assay	Bone Marrow Cells of Male Mice	up to 5000 mg/kg	Negative for increases in chromosomal aberrations.

Carcinogenicity Studies

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

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18. Product Monograph ZESTRIL (AstraZeneca Canada Inc.), Date of Revision: November 17, 2009; Control No: 130884