PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-LISINOPRIL

Lisinopril Tablets

Tablets, 5 mg, 10 mg and 20 mg, oral administration

USP

Angiotensin Converting Enzyme Inhibitor

APOTEX INC.
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Toronto, Ontario
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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	08/2024
7 WARNINGS AND PRECAUTIONS	08/2024

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-LISINOPRIL (lisinopril tablets) is indicated in adults for:

- Hypertension: in the treatment of essential hypertension and in renovascular hypertension, alone or in combination with thiazide diuretics. A great majority of patients (>80%) with severe hypertension required combination therapy.

- Heart Failure: in the management of symptomatic congestive heart failure as adjunctive treatment with diuretics, and where appropriate, digitalis. Treatment with APO-LISINOPRIL should be initiated under close medical supervision, usually in a hospital. High doses of APO-LISINOPRIL reduce the risk of the combined outcomes of mortality and hospitalization (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

- Acute Myocardial Infarction: 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 APO-LISINOPRIL should be reassessed after 6 weeks. If there is no evidence of symptomatic or asymptomatic left ventricular dysfunction, treatment with APO-LISINOPRIL can be stopped.
  APO-LISINOPRIL should not be used if systolic blood pressure is <100 mmHg, if clinically relevant renal failure is present, or if there is a history of bilateral stenosis of the renal arteries (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension Following Acute Myocardial Infarction and Renal, Renal Impairment).

1.1 Pediatrics

Pediatrics (6 to 16 years old): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of lisinopril tablets in pediatric patients aged 6 to 16 years old with GFR >60 mL/min/1.73 m^2 has been established. Therefore, Health Canada has authorized an indication for this age category in hypertensive patients (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.3 Pediatrics).

Pediatrics (< 6 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use in this age group (see 4.2 Recommended Dose and Dosage Adjustment and 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril tablets (see 7.1.4 Geriatrics). Pharmacokinetic studies indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients (See 4. DOSAGE AND

ADMINISTRATION).

2 CONTRAINDICATIONS

APO-LISINOPRIL (lisinopril tablets USP) is contraindicated in patients who:

- are hypersensitive to the drug or to any ingredient in the formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGHTS, COMPOSITION, AND PACKAGING section of the product monograph;
- have a known allergy to angiotensin converting enzyme (ACE) inhibitors;
- have a history of hereditary/idiopathic angioedema, or angioedema related to previous treatment with an ACE inhibitor (see 7 WARNINGS AND PRECAUTIONS, Immune);
- are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraception (see 7.1.1 Pregnant Women and 8 ADVERSE REACTIONS);
- are nursing (see 7.1.2 Breast-feeding);
- are taking sacubitril/valsartan due to an increased risk of angioedema. APO-LISINOPRIL must not be initiated until at least 36 hours have elapsed following discontinuation of salcubitril/valsartan therapy. If treatment with APO-LISINOPRIL is stopped, sacubitril/valsartan therapy must not be initiated until 36 hours after the last dose of APO-LISINOPRIL.
- are taking aliskiren-containing drugs and have:
  - diabetes mellitus (type 1 or 2)
  - moderate to severe renal impairment (GFR < 60 mL/min/1.73 m^2)
  - hyperkalemia (> 5mMol/L) or
  - congestive heart failure who are hypotensive (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Renal, and 9.4 Drug-Drug Interactions);
- Are taking angiotensin receptor blockers (ARBs) or other ACE inhibitors and have:
  - diabetes mellitus (type 1 or type 2) with end organ damage,
  - moderate to severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2),
  - hyperkalemia (> 5mMol/L) or
  - congestive heart failure and are hypotensive (see 9.4 Drug-Drug Interactions);
- Are less than 6 years of age;
- Are 6 to 16 years of age with severe kidney insufficiency (GFR < 60 mL/min/1.73 m^2).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

When used in pregnancy, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected, APO-LISINOPRIL should be discontinued as soon as possible (see 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

Essential Hypertension

In patients with essential hypertension, not on diuretic therapy, the usual recommended starting dose is 10 mg once a day. The usual dosage range is 10 to 40 mg per day, administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. The maximum dose used in long-term controlled clinical trials was 80 mg/day. If blood pressure is not controlled with APO-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 APO-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 APO-LISINOPRIL. The diuretic should be discontinued, if possible, for 2 to 3 days before beginning therapy with APO-LISINOPRIL to reduce the likelihood of hypotension (see 7 WARNINGS AND PRECAUTIONS). The dosage of APO-LISINOPRIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with APO-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 ≥2 hours and until blood pressure has stabilized for ≥1 additional hour (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS, Hypotension).

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: **Table 1: Starting dose in patients with renal impairment**

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.

Dosage Adjustments in Special Populations

Pediatric Patients (6 to 16 years old)

For patients who can swallow tablets, the dose should be individualized according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. APO-LISINOPRIL is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg (see 7.1.3 Pediatrics, 10.2 Pharmacodynamics and 10.3 Pharmacokinetics).

APO-LISINOPRIL is not recommended in pediatric patients <6 years or with GFR <30 mL/min/1.73 m^2 (see 10.2 Pharmacodynamics and 10.3 Pharmacokinetics).

Geriatrics (> 65 years of age)

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril tablets. 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 7.1.4 Geriatrics).

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 increased risk of severe hypotension and renal insufficiency to the first dose of APO-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

APO-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 APO-LISINOPRIL, because severe hypotension and, more rarely, consequent renal failure have been reported (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and Renal).

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 APO-LISINOPRIL dose should be increased:

- by increments of ≤10 mg,
- at intervals of ≥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 APO-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 1 INDICATIONS).

The first dose of APO-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 APO-LISINOPRIL must not be initiated in patients who are at risk of serious hemodynamic deterioration (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). After 3 days, if hypotension occurs (systolic blood pressure ≤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 <90 mmHg for >1 hour), APO-LISINOPRIL should be withdrawn.

Renal function should be assessed before and during therapy with APO-LISINOPRIL (see 7 WARNINGS AND PRECAUTIONS, Renal).

Dosing should normally continue for 6 weeks. At that time, patients with signs or symptoms of heart failure should continue with APO-LISINOPRIL (see 4 DOSAGE AND ADMINISTRATION).

APO-LISINOPRIL is compatible with intravenous or transdermal glyceryl trinitrate.

4.4 Administration

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

4.5 Missed Dose

If the patient misses a dose during the day, they should be advised to continue with the next one at the usual time and advised never to double the dose.

5 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 7 WARNINGS AND PRECAUTIONS, Immune). Serum electrolytes and creatinine should be monitored frequently.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Use	Tablet: 5 mg, 10 mg and 20 mg	Anhydrous lactose, red ferric oxide and zinc stearate.

APO-LISINOPRIL 5 mg tablets are pink, oval, biconvex tablets engraved ‘APO’ over ‘L5’ on one side and scored on the other. Available in bottles of 100 and 500.

APO-LISINOPRIL 10 mg tablets are pink, oval, biconvex tablets engraved ‘APO’ over ‘L10’ on one side. Available in bottles of 100 and 500.

APO-LISINOPRIL 20 mg tablets are deep pink, oval, biconvex tablets engraved ‘APO’ over ‘L20’ on one side. Available in bottles of 100 and 500.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS.

Cardiovascular

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin converting enzyme (ACE) inhibitors, such as lisinopril tablets, or of angiotensin receptor antagonists (ARBs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 mL/min/1.73 m^2). Therefore, the use of APO-LISINOPRIL in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).

Further, co-administration of ACE inhibitors, including APO-LISINOPRIL, with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, decreased renal function (including acute renal failure), and hyperkalemia.

Avoid the concomitant use of ACE inhibitors and ARBs in patients with diabetic nephropathy.

If dual blockade therapy is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Hypotension

Symptomatic hypotension has occurred after administration of lisinopril tablets, 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 4 DOSAGE AND ADMINISTRATION). In patients with severe CHF, 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 2 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 8 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 APO-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 APO-LISINOPRIL discontinuation (see 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINSTRATION).

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

Hypotension Following Acute Myocardial Infarction

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

These include patients with systolic blood pressure of ≤100 mmHg or 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 4 DOSAGE AND ADMINSTRATION).

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

Valvular Stenosis, Hypertrophic Cardiomyopathy

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

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

Driving and Operating Machinery

Occupation Hazards

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

Ear/Nose/Throat

Cough

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

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

Endocrine and Metabolism

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with APO-LISINOPRIL (See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

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 CHF. 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 10. CLINICAL PHARMACOLOGY), high dose (≤35 mg) versus low dose (≤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 (e.g., spironolactone, triamterene or amiloride), potassium supplements, other drugs that may increase potassium levels (e.g., heparin, co-trimoxazole) and/or potassium- containing salt substitutes (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Hematologic

Neutropenia/Agranulocytosis

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

Hepatic/Biliary/Pancreatic

Patients with Impaired Liver Function

Hepatitis, either hepatocellular or cholestatic, jaundice, marked elevations of liver enzymes and/or serum bilirubin have occurred during therapy with lisinopril tablets in patients with or without pre-existing liver abnormalities (see 8 ADVERSE REACTIONS). Very rarely, it has been reported that in some patients the undesirable development of hepatitis has progressed to hepatic failure. Patients receiving APO-LISINOPRIL who develop jaundice or marketed elevation of hepatic enzymes should discontinue APO-LISINOPRIL and receive appropriate medical follow-up (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic). Should the patient receiving APO-LISINOPRIL experience any unexplained symptoms, 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 APO-LISINOPRIL should be considered when appropriate.

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

Immune

Angioedema

Angioedema has been uncommonly reported in patients treated with lisinopril tablets and may occur at any time during therapy. Angioedema associated with laryngeal or tongue edema and/or shock may be fatal. If angioedema occurs, APO-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 2 CONTRAINDICATIONS).

Patients receiving coadministration of ACE inhibitor with a mTOR (mammalian target of rapamycin) inhibitor (e.g., temsirolimus, sirolimus, everolimus), a neutral endopeptidase (NEP) inhibitor, or tissue plasminogen activator may be at increased risk for angioedema. Caution should be used when either initiating ACE inhibitor therapy in patients already taking a mTOR inhibitor, or a NEP inhibitor or vice versa. Monitor patients for potential development of angioedema after initiation of tissue plasminogen activator infusion (see 9 DRUG INTERACTIONS).

Patients co-administered ACE inhibitor and dipeptidyl peptidase IV (DPP-IV) inhibitors (e.g. alogliptin, linagliptin, saxagliptin, and sitagliptin) may be at increased risk for angioedema (See 9 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.

Nitritoid Reactions – 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 (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Peri-Operative Considerations

Surgery/Anesthesia

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

corrected by volume expansion.

Renal

Renal Impairment

As a consequence of inhibiting the RAAS, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the RAAS, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe CHF, 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.

The use of ACE inhibitors, including APO-LISINOPRIL, or ARBs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR <60 mL/min/1.73 m^2) (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS and 9.4 Drug-Drug Interactions).

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

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

7.1 Special Populations

7.1.1 Pregnant Women

ACE inhibitors are contraindicated during pregnancy because these agents can cause fetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, APO-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.

7.1.2 Breast-feeding

The presence of concentrations of ACE inhibitor have been reported in human milk. Use of ACE inhibitors is contraindicated during breast-feeding.

7.1.3 Pediatrics

Pediatrics (6 to 16 years old): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of lisinopril tablets in hypertensive pediatric patients aged 6 to 16 years old with GFR >60 mL/min/1.73 m^2 has been established. Therefore, Health Canada has authorized an indication for this pediatric age group. (see 4 DOSAGE AND ADMINISTRATION, 10.2 Pharmacodynamics and 10.3 Pharmacokinetics)

Pediatrics (<6 years old): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for this pediatric age group.

The safety and efficacy of lisinopril tablets in pediatric patients has not been determined in heart failure or acute myocardial infarction.

7.1.4 Geriatrics

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril tablets. 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.

Ethnic Origin
Race
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent clinical adverse reactions were: dizziness (4.4%), headache (5.6%), asthenia/fatigue (2.7%), diarrhea (1.8%) and cough (3.0%). Discontinuation of therapy was required in 5.9% of patients.

For adverse reactions which occurred in hypertensive patients and patients with CHF treated with lisinopril tablets in controlled clinical trials, comparative incidence data are listed in 8.2 Clinical Trial Adverse Reactions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3: Incidence of Adverse Reactions Occurring in Patients Treated with Lisinopril Tablets In Controlled Clinical Trials.

		Hypertension n=2633 (%)	Congestive Heart Failure n=636 (%)
Cardiovascular	Hypotension	0.8	5.2
	orthostatic effects	0.9	1.3
	chest pain	1.1	7.4
	angina	0.3	3.8
	edema	0.6	2.5
	palpitation	0.8	1.9
	rhythm disturbances	0.5	0.6
Gastrointestinal	Diarrhea	1.8	6.1
	Nausea	1.9	4.9
	Vomiting	1.1	2.4
	Dyspepsia	0.5	1.9
	Anorexia	0.4	1.4
	Constipation	0.2	0.8
	flatulence	0.3	0.5
Nervous System	Dizziness	4.4	14.2
	Headache	5.6	4.6
	Paresthesia	0.5	2.8
	Depression	0.7	1.1

		Hypertension n=2633 (%)	Congestive Heart Failure n=636 (%)
	Somnolence	0.8	0.6
	Insomnia	0.3	2.4
	vertigo	0.2	0.2
Respiratory	Cough	3.0	6.4
	Dyspnea	0.4	7.4
	orthopnea	0.1	0.9
Dermatologic	Rash	1.0	5.0
	pruritus	0.5	1.4
Musculoskeletal	muscle cramps	0.5	2.2
	back pain	0.5	1.7
	leg pain	0.1	1.3
	shoulder pain	0.2	0.8
Other	asthenia/fatigue	2.7	7.1
	blurred vision	0.3	1.1
	fever	0.3	1.1
	flushing	0.3	0.3
	gout	0.2	1.7
	decreased libido	0.2	0.2
	malaise	0.3	1.1

Angioedema

Angioedema has been reported in patients receiving lisinopril tablets (0.1%). In very rare cases, intestinal angioedema has been reported (see 7 WARNINGS AND PRECAUTIONS, Immune).

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 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

In patients with CHF, 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 10 CLINICAL PHARMACOLOGY), high dose (≤35 mg) versus low

dose (≤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) 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:

Table 4: Incidence of Adverse Reactions Occurring in Patients Treated with Lisinopril Tablets In Controlled Clinical Trials.

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

Event	Control n=4729	Lisinopril n=4713	Lisinopril + GTN n=4722	GTN Alone n=4731
Late CHF (>4 days)	4.5	4.5	4.2	4.2

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (6 to 16 years old): The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Serum Electrolytes

Hyperkalemia (see 7 WARNINGS AND PRECAUTIONS).

Creatinine, Blood Urea Nitrogen Increases in blood urea nitrogen (BUN) 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 tablets alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see 7 WARNINGS AND PRECAUTIONS). In patients with CHF on 2.5 to 20 mg lisinopril and concomitant diuretic therapy, reversible increases in BUN (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 10 CLINICAL PHARMACOLOGY), high dose (≤35 mg) versus low dose (≤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 tablets 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 ACE inhibitors, including lisinopril. Several cases of agranulocytosis and neutropenia have been reported in which a causal relationship to lisinopril cannot be excluded (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Hepatic

Elevations of liver enzymes and/or serum bilirubin have occurred (see 7 WARNINGS AND PRECAUTIONS, Hepatic, Biliary/Pancreatic).

Discontinuations

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

8.5 Post-Market Adverse Reactions

The following undesirable effects have been observed and reported during treatment with lisinopril tablets 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: agranulocytosis, anemia, bone marrow depression, hemolytic anemia (see 7 WARNINGS AND PRECAUTIONS, Hematologic), leucopenia, thrombocytopenia.

Cardiac and vascular disorders

Common: orthostatic effects (including hypotension) (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular), 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular) palpitations, tachycardia.

Endocrine disorders

Rare: inappropriate antidiuretic hormone secretion

Gastrointestinal disorders

Common: diarrhea, vomiting.

Uncommon: abdominal pain, indigestion, nausea.

Rare: dry mouth.

Very rare: intestinal angioedema (See 7 WARNINGS AND PRECAUTIONS, Immune and 8 ADVERSE REACTIONS), pancreatitis.

General disorders and administration site conditions

Uncommon: asthenia, fatigue.

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 APO-LISINOPRIL who develop jaundice or marketed elevation of hepatic enzymes should discontinue APO-LISINOPRIL and receive appropriate medical follow-up (See 7 WARNINGS AND PRECAUTIONS, Hepatic, Biliary/Pancreatic).

Immune system disorders

Not known: anaphylactic/anaphylactoid reaction

Investigations

Uncommon: increases in blood urea, increases in serum creatinine (see 7 WARNINGS AND PRECAUTIONS), increases in liver enzymes (see 7 WARNINGS AND PRECAUTIONS, Hepatic, Biliary/Pancreatic).

Rare: decreases in hemoglobin, decreases in hematocrit, increases in serum bilirubin (see 7 WARNINGS AND PRECAUTIONS, Hepatic, Biliary/Pancreatic).

Metabolism and nutrition disorders

Uncommon: hyperkalemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Rare: hyponatremia.

Very rare: hypoglycemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Nervous system and psychiatric disorders

Common: dizziness, headache.

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

Rare: mental confusions, olfactory disturbance.

Renal and urinary disorders

Common: renal dysfunction.

Rare: acute renal failure, uremia.

Very rare: oliguria/anuria (see 7 WARNINGS AND PRECAUTIONS, Renal).

Reproductive system and breast disorders

Uncommon: impotence.

Respiratory, thoracic and mediastinal disorders:

Common: cough.

Uncommon: rhinitis.

Very rare: bronchospasm, sinusitis.

Skin and subcutaneous tissue disorders

Uncommon: rash, pruritis, hypersensitivity/angioedema: angioedema of the face, extremities, lips, tongue, glottis, and/or larynx (see 7 WARNINGS AND PRECAUTIONS, Immune).
Rare: alopecia, psoriasis, urticaria.
Very rare: cutaneous pseudolymphoma, diaphoresis, erythema multiforme, pemphigus, Stevens - Johnson Syndrome, toxic epidermal necrolysis.

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Combination with sacubitril/valsartan; see 2 CONTRAINDICATIONS;
- Combination with aliskiren-containing drugs; see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS and 9.4 Drug-Drug Interactions;
- Combination with angiotensin receptor blockers (ARBs) or other ACE inhibitors; see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions.

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5: Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Agents Causing Renin Release (e.g. diuretics)	CT	The antihypertensive effect of lisinopril tablets is augmented by antihypertensive agents that cause renin release.	Caution is warranted.

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Agents Affecting Sympathetic Activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents)	CT	Beta-adrenergic blocking drugs add some further antihypertensive effect to lisinopril.	Use with caution.
Aliskiren-containing medicines	CT	Dual blockade of the Renin-Angiotensin-Aldosterone system (RAAS) with ACE inhibitors and aliskiren-containing drugs has been associated with an increased incidence of severe hypotension, decreased renal function (including acute renal failure), and hyperkalemia when compared to the use of a single RAS-acting agent.	Dual blockade of the Renin Angiotensin-Aldosterone system (RAAS) with ACE inhibitors and aliskiren-containing drugs is contraindicated in patients with: – diabetes mellitus (type 1 or 2) – moderate to severe renal impairment (GFR < 60 mL/min/1.73 m^2) – hyperkalemia (> 5mMol/L) or – congestive heart failure who are hypotensive. It is not recommended in all other patients. (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Renal, and 9.4 Drug-Drug Interactions).
Angiotensin receptor blockers (ARBs)	CT	Dual blockade of RAAS with ACE inhibitors and ARBs has been associated with an increased incidence of severe hypotension, decreased renal function (including acute renal failure), and hyperkalemia	Dual blockade of RAAS with ACE inhibitors and ARBs is contraindicated in patients with: – diabetes with end organ damage, – moderate to severe kidney insufficiency (GFR

Proper/ Common name	Source of Evidence	Effect	Clinical comment
		when compared to the use of a single RAS-acting agent.	< 60 mL/min/1.73 m^2), – hyperkalemia (> 5mMol/L) or – congestive heart failure who are hypotensive It is not recommended in all other patients (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, and 9.4 Drug-Drug Interactions);
Antihypertensive Therapy	CT	When lisinopril is given to patients already treated with other antihypertensive agents, further falls in blood pressure may also occur.	Caution is warranted.
Antidiabetic agents (e.g. insulin, oral hypoglycemic agents)	CT	Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycemia.	Monitor diabetic patients closely (see 7 WARNINGS AND PRECAUTIONS)
Diuretic Therapy	CT	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 7 WARNINGS AND PRECAUTIONS, Hypotension and 4 DOSAGE AND

Proper/ Common name	Source of Evidence	Effect	Clinical comment
			ADMINISTRATION).
DPP-IV inhibitors (e.g. alogliptin, linagliptin, saxagliptin, sitagliptin)	C	Patients taking concomitant DPP-IV inhibitors may be at increased risk for angioedema.	Use caution when initiating ACE inhibitor therapy in patients already receiving a DPP-IV inhibitor or vice versa (See 7 WARNINGS AND PRECAUTIONS)
Gold	C	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.	Caution is warranted.
Lithium Salts	CT	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.
Mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus)		Concomitant treatment of ACE inhibitors with mTOR inhibitors increases the incidence of angioedema	Use caution when initiating therapy with ACE or mTOR inhibitor in patients already taking either mTOR or ACE inhibitor, respectively (See 7 WARNINGS AND PRECAUTIONS)
Neutral endopeptidase (NEP) inhibitor		Concomitant therapy with a NEP inhibitor may increase the risk for angioedema caused by ACE inhibitors.	Use caution when initiating ACE inhibitor therapy in patients already taking a NEP inhibitor, or vice versa (See 7 WARNINGS AND PRECAUTIONS)

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)	CT	In some patients with compromised renal function, lisinopril co-administration with NSAIDs may produce further renal function deterioration. Indomethacin may diminish the antihypertensive efficacy of concomitantly administered APO-LISINOPRIL.	Caution is warranted.
Potassium Supplements, potassium-sparing agents or potassium-containing salt substitutes and other drugs that may increase serum potassium levels	T	Lisinopril decreases aldosterone production, elevation of serum potassium may occur.	Potassium sparing diuretics such as spironolactone, triamterene or amiloride, potassium supplements and other drugs that may increase potassium levels (e.g., heparin, co-trimoxazole) 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.
Tissue plasminogen activators		Concomitant treatment of ACE inhibitors tissue plasminogen activator may increase the risk of angioedema	Monitor patients for potential development of angioedema after initiation of tissue plasminogen activator infusion. (See 7 WARNINGS AND PRECAUTIONS, Immune).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

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 potassium. In patients treated with lisinopril tablets and a thiazide diuretic there was essentially no change in serum potassium (see 7 WARNINGS AND PRECAUTIONS).

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

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

Table 6: 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) mcg/kg

Study	Species/Strain	Number of Animals/Group	Route	Dose	Results
duration of ACE inhibitory activity of lisinopril in rats**	male Sprague/Dawley	4	i.v.	3 & 10 mcg/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 mcg/kg	ID_{50} = 6.5 mcg/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.

10.2 Pharmacodynamics

Hypertension

Adults

Administration of lisinopril tablets to patients with hypertension results in a reduction of both supine and standing blood pressure. Abrupt withdrawal of lisinopril tablets 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 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 9 hypertensive patients, following administration of lisinopril tablets, 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 tablets on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

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

Congestive heart failure

Administration of lisinopril tablets 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 tablets ≤35 mg once daily reduced the risk of the combined outcome of mortality and hospitalization in patients with chronic congestive heart failure (CHF). The ATLAS study was an international, multicenter, double-blind, parallel group clinical trial which evaluated the effects of low doses, 2.5 mg to 5.0 mg, versus high doses, 32.5 mg to 35.0 mg lisinopril tablets on mortality and morbidity in patients with chronic CHF. 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 6 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 tablets was associated with an 11.6% (p=0.002) risk reduction over low dose (2.5 and 5 mg). High dose lisinopril tablets 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).

Pediatrics (6 to 16 years old)

In a clinical study involving 115 hypertensive pediatric patients 6 to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5, or 20 mg of lisinopril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of lisinopril daily. At the end of 2 weeks, lisinopril administered once daily lowered trough blood pressure in a dose-dependent manner with consistent antihypertensive efficacy demonstrated at doses >1.25 mg (0.02 mg/kg). This effect was confirmed in a withdrawal phase, where the diastolic pressure rose by about 9 mmHg more in patients randomized to placebo than it did in patients who were randomized to remain on the middle and high doses of lisinopril. The dose-dependent antihypertensive effect of lisinopril was consistent across several demographic subgroups: age, Tanner stage, gender, race. In this study, lisinopril was generally well-tolerated.

10.3 Pharmacokinetics

Absorption:
After oral administration of lisinopril tablets, 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.

Based on urinary recovery, the extent of absorption of lisinopril is approximately 25%, with large inter-subject variability (6 to 60%) at all doses tested (5 to 80 mg).

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

Distribution:
Lisinopril does not bind serum proteins other than ACE.

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

Metabolism:
Lisinopril does not undergo metabolism and is excreted unchanged entirely in the urine.

Elimination:
Lisinopril can be removed by dialysis.

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

Special Populations and Conditions

- **Pediatrics (6 to 16 years old):** The pharmacokinetics of lisinopril were studied in 29 pediatric hypertensive patients between 6 years and 16 years with GFR >30 mL/min/1.73 m^2. After doses of 0.1 to 0.2 mg/kg, steady state peak plasma concentrations of lisinopril occurred within 6 hours and the extent of absorption based on urinary recovery was about 28%. These values are similar to those obtained previously in adults. The typical value of lisinopril oral clearance (systemic clearance/absolute bioavailability) in a child weighing 30 kg is 10 L/h, which increases in proportion to renal function.

- **Geriatrics (≥65 years):** In a study in elderly healthy subjects (≥65 years), a single dose of lisinopril 20 mg produced higher serum concentrations and higher values for the area under the plasma curve (AUC) 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 CHF.

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 CHF. Renal clearance of lisinopril was decreased in the elderly, particularly in the presence of CHF.

- **Renal Insufficiency:** Impaired renal function decreases elimination of lisinopril. This decrease becomes clinically important when the glomerular filtration rate (GFR) is <30 mL/min (see 7 WARNINGS AND PRECAUTIONS, Renal, and 4 DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

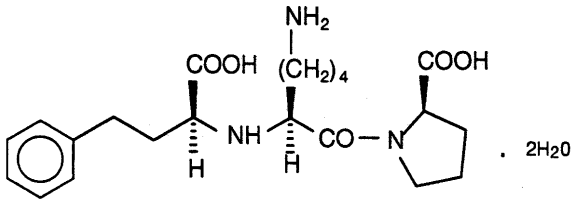
Drug Substance

Proper name: Lisinopril

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

Molecular formula and molecular mass: $C_{21}H_{31}N_3O_5 \cdot 2H_2O$, 441.53 g/mol

Structural formula:



Physicochemical properties: Lisinopril is a white, crystalline powder which melts at about 160°C with decomposition. It is soluble in water, sparingly soluble in methanol and practically insoluble in ethanol.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A randomized, single-dose, three-period, three-treatment crossover comparative bioavailability study of APO-LISINOPRIL 40 mg tablets (Apotex Inc.), APO-LISINOPRIL 10 mg tablets (Apotex Inc.), and ZESTRIL 10 mg tablets (Astra Zeneca Pharma) was conducted in twenty-seven (27) healthy human male volunteers under fasting conditions. A summary of the bioavailability data comparing APO-LISINOPRIL 1 x 40 mg tablets (Apotex Inc.) and ZESTRIL 4 x 10 mg tablets (Astra Zeneca Pharma) from 25 subjects that were included in the statistical analysis were presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Lisinopril (1 x 40 mg vs. 4 x 10 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	2315.12 2434.25 (33.66)	2549.25 2697.64 (36.52)	90.8	81.6-101.0
AUC_I (ng·h/mL)	2357.37 2475.30 (33.33)	2593.51 2739.51 (36.04)	90.9	81.8-100.9
C_{max} (ng/mL)	165.19 174.69 (37.23)	183.45 197.24 (42.17)	90.1	80.3-101.1
T_{max}[3] (h)	6.00 (5.00 -8.00)	6.00 (4.00 -8.00)		
$T_{1/2}$[4] (h)	8.35 (32.29)	8.31 (31.64)		

[1] APO-LISINOPRIL (lisinopril tablets), 40 mg (Apotex Inc.)
[2] ZESTRIL (lisinopril tablets) Tablets, 4 X 10 mg (Astra Zeneca Pharma)
[3] Expressed as median (range) only
[4] Expressed as the arithmetic mean (CV %) only

A randomized, single-dose, three-period, three-treatment crossover comparative bioavailability study of APO-LISINOPRIL 40 mg tablets (Apotex Inc.), APO-LISINOPRIL 10 mg tablets (Apotex Inc.), and ZESTRIL 10 mg tablets (Astra Zeneca Pharma) was conducted in twenty-seven (27) healthy human male volunteers under fasting conditions. A summary of the results comparing APO-LISINOPRIL 4 x 10 mg tablets (Apotex Inc.) and ZESTRIL 4 x 10 mg tablets (Astra Zeneca Pharma) from 25 subjects that were included in the statistical analysis were presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Lisinopril (4 x 10 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	2485.07 2577.52 (29.33)	2549.25 2697.64 (36.52)	97.5	87.6-108.5

Lisinopril (4 x 10 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_I (ng·h/mL)	2529.34 2619.70 (28.88)	2593.51 2739.51 (36.04)	97.5	87.8 – 108.3
C_{max} (ng/mL)	180.78 187.72 (31.61)	183.45 197.24 (42.17)	98.5	87.8 – 110.6
T_{max}[3] (h)	6.00 (5.00 -8.00)	6.00 (4.00 -8.00)		
$T_{1/2}$[4] (h)	8.11 (25.90)	8.31 (31.64)		

[1] APO-LISINOPRIL (lisinopril tablets), 10 mg (Apotex Inc.)
[2] ZESTRIL (lisinopril tablets) Tablets, 10 mg (Astra Zeneca Pharma)
[3] Expressed as median (range) only
[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

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.

Table 7: 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 supplementation prevented decreased weight gain and elevations in serum urea nitrogen at 30 and 60 mg.

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
				saline)	Decreases in cardiac weight at 30 and 60 mg, were suppressed by saline supplementation in males at 30 mg. At 30 and 60 mg renal changes produced due to a low salt diet, (renal tubular degeneration and renal tubular basophilia) were prevented by saline supplementation. Mild gastric erosions or necrotic changes were seen in 1 or 2 of 30 rats given 30 or 60 mg. These gastric changes were not seen in saline supplemented animals given these doses; however, the relationship of amelioration due to saline is uncertain because of the low incidence of this change, which is also occasionally seen in untreated animals.
Rat	5 Days 6 Day Recovery	8 M	Oral	5, 300	Consumption of 2% saline increased during treatment at 5 mg and on Days 2 to 4 post-treatment at 300 mg.
Dog	2-Week	3 F + 3 M	Oral	3, 10, 30	At 30 mg, slight mineralization of the papilla muscle of the heart was seen in 1 of 6 dogs.
Dog	3-Month with 1-Month Interim	5 F + 5 M	Oral	3, 10, 30	At 10 mg, hemoglobin concentration, hematocrit, and erythrocyte count decreased in 2 dogs. Marked increases in serum urea nitrogen and creatinine were observed in 2 of 10 dogs. One of these dogs had marked renal tubular degeneration and ulcers of the tongue, gums, and gastric pyloric mucosa related to uremia. At 30 mg there was an increase in serum urea nitrogen (average up to 2-fold) and a decrease in serum sodium (down to 4 mEq/L) and serum chloride (down to 3 mEq/L). At 10 and 30 mg, average cardiac weight 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

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
					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 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	Oral	3, 10, 30 and 100	Eight of 16 dogs given 100 mg died or were killed because of poor physical condition. One of 6 dogs given 30 mg was killed because of poor physical condition. At 10 mg or greater increased BUN and dilation of renal tubules was seen. Fatty degeneration of renal tubular epithelium occurred at the 2 highest dosage levels. The changes are reversible as only slight dilation of renal tubules was present in some animals given 100 mg after 4 weeks of recovery.

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Effects
		5 M + 5 F			
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.

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

Table 8: Carcinogenicity

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

Species	Duration	No. of Animals/Group	Route	Dose mg/kg/day	Results
					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.

Table 9: Genotoxicity

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

Reproductive and Developmental Toxicology:

Lisinopril was not teratogenic in mice treated on days 6 to 15 of gestation with ≤1000 mg/kg/day (625x the maximum recommended human dose). There was an increase in fetal resorptions at doses ≥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 ≤300 mg/kg/day (188x the maximum recommended dose) of lisinopril at days 6 to 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 to 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 ≤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.

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.

Table 10: 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

Species	No. of Animals/Group	Dose mg/kg/day	Route	Duration of Dosing	Results
					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.

Table 11: 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ZESTRIL® (Lisinopril Tablets, 5 mg, 10 mg and 20 mg), submission control 268405, Product Monograph, Searchlight Pharma Inc, (NOV 23, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-LISINOPRIL

Lisinopril Tablets

Read this carefully before you start taking **APO-LISINOPRIL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-LISINOPRIL**.

Serious Warnings and Precautions

- APO-LISINOPRIL should not be used during pregnancy. Taking it during pregnancy can cause injury or even death to your baby. If you discover that you are pregnant while taking APO LISINOPRIL, stop the medication and contact your healthcare professional as soon as possible.

What is APO-LISINOPRIL used for?

APO-LISINOPRIL is used in adults:

- To treat high blood pressure (hypertension);
- With other medications to treat heart failure, where the heart does not pump your blood around your body as well as it should;
- To lower the risk of having a heart attack (myocardial infarction) in patients who have already had a heart attack.

APO-LISINOPRIL is used in children (6 to 16 years of age) to treat high blood pressure.

How does APO-LISINOPRIL work?

APO-LISINOPRIL belongs to a group of medicines called angiotensin converting enzyme (ACE) inhibitors. You can recognize ACE inhibitors because their medicinal ingredient ends in '-**PRIL**'.

APO-LISINOPRIL works by widening your blood vessels, which makes it easier for your heart to pump blood to all parts of your body. This helps to lower blood pressure.

This medicine does not cure your disease, but helps to control it. Therefore, it is important to continue taking APO-LISINOPRIL regularly even if you feel fine.

What are the ingredients in APO-LISINOPRIL?

Medicinal ingredients: Lisinopril

Non-medicinal ingredients: Anhydrous lactose, red ferric oxide, and zinc stearate.

APO-LISINOPRIL comes in the following dosage forms:

Tablets: 5 mg, 10 mg and 20 mg.

Do not use APO-LISINOPRIL if:

- You are allergic to lisinopril or to any non-medicinal ingredient in the formulation.
- You have a family history of angioedema (allergic reaction), or have ever had an allergic reaction to any other ACE inhibitor. Be sure to tell your healthcare professional that this has happened to you.
- You are taking sacubitril/valsartan (Entresto®), due to the increased risk of serious allergic reaction which causes swelling of the face or throat (angioedema) when taken with APO-LISINOPRIL.
- You are pregnant or intend to become pregnant. Taking APO-LISINOPRIL during pregnancy can cause injury or even death to your baby.
- You are breastfeeding. APO-LISINOPRIL passes into breast milk.
- You are already taking a blood pressure-lowering medicine containing aliskiren (such as Rasilez) and you have one of the following conditions:
  - diabetes
  - kidney disease
  - high potassium levels
  - heart failure combined with low blood pressure

- You are taking an angiotensin receptor blocker (ARB), another medicine to treat your high blood pressure, or another ACE inhibitor and have one of the following conditions:
  - diabetes with end organ damage
  - kidney disease
  - high potassium levels
  - heart failure combined with low blood pressure

  You can recognize ARBs because their medicinal ingredient ends in "-**SARTAN**".

- You are 6 to 16 years old with severe kidney problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-LISINOPRIL. Talk about any health conditions or problems you may have,

including if you:

- Are allergic to any drug used to lower blood pressure.
- Have recently received or are planning to get allergy shots for bee or wasp stings.
- Have narrowing of an artery or a heart valve.
- Have had a heart attack or stroke.
- Have heart failure.
- Have diabetes, liver or kidney disease.
- Are on dialysis.
- Are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Are on a low-salt diet.
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with APO-LISINOPRIL is not recommended.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-**SARTAN**".
- Are receiving gold (sodium aurothiomalate) injections.

Other warnings you should know about:

Monitoring: During your treatment with APO-LISINOPRIL, your healthcare professional may check your kidney and liver function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

Exposure to sunlight: You may become sensitive to the sun while taking APO-LISINOPRIL. Limit your exposure to sunlight until you know how you respond.

Use of anesthesia: If you are going to have surgery and will be given an anesthetic, be sure to tell your healthcare professional that you are taking APO-LISINOPRIL.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to APO-LISINOPRIL. Dizziness, light-headedness, or fainting can occur, especially after the first dose and when the dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

- Sacubitril/valsartan.
- Medicines containing aliskiren, ARBs or other ACE inhibitors if you also have:
  - Diabetes (with or without end organ damage),
  - Kidney disease,

- High potassium levels, or
- Heart failure with low blood pressure.

The following may also interact with APO-LISINOPRIL:

- Agents increasing serum potassium, such as a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill").
- Allopurinol used to treat gout.
- Drugs to treat diabetes such as:
  - Insulin,
  - Medicines known as dipeptidyl peptidase IV (DPP-IV) inhibitors, these include alogliptin, linagliptin, saxagliptin and sitagliptin,
  - Other oral medications (such as sulphonylureas).

  Your dose of these types of drugs may need to be changed when taking them in combination with APO-LISINOPRIL.
- Drugs used to treat cancer such as, temsirolimus and everolimus.
- Gold for the treatment of rheumatoid arthritis.
- Lithium used to treat bipolar disease.
- Non-steroidal anti-inflammatory medicines (NSAIDs), used to reduce pain and swelling. These include ibuprofen, naproxen, and celecoxib.
- Blood pressure-lowering drugs, including diuretics ("water pills"), aliskiren-containing products (such as Rasilez), or angiotensin receptor blockers (ARBs).
- Medicines known as mammalian target of rapamycin (mTOR) inhibitors such as sirolimus, a drug used to prevent the organ rejection after a transplant.
- Medicines known as tissue plasminogen activators (tPA), these are used to dissolve blood clots that have formed in blood vessels.
- Medicines known as neutral endopeptidase (NEP) inhibitors.

How to take APO-LISINOPRIL:

- Take APO-LISINOPRIL exactly as prescribed.
- It is recommended to take your dose at about the same time every day.
- Swallow the tablet with a drink of water. It does not matter if you take APO-LISINOPRIL before or after food.
- Do NOT stop taking APO-LISINOPRIL unless your healthcare professional tells you to, even if you are feeling better.

Usual dose:

Your healthcare professional has decided the best dose for you. Take your dose once daily, exactly as your healthcare professional has told you to.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-LISINOPRIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not take a double dose.

What are possible side effects from using APO-LISINOPRIL?

These are not all the possible side effects you may have when taking APO-LISINOPRIL. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- dizziness (or light-headedness), drowsiness, fatigue, headache, tiredness, weakness (loss of strength)
- cough, running nose
- itching, psoriasis, sinus pain, skin rash, wheezing
- abdominal pain, diarrhea, nausea, stomach pain and indigestion, vomiting
- confusion, feeling sleepy or difficulty in going to sleep, mood changes (including signs of depression), seen and/or heard hallucinations, strange dreams
- changes in the way things smell or taste, dry mouth, numbness or tingling in the fingers or toes
- rapid heartbeat
- impotence
- hair loss

In patients with high blood pressure, fainting is uncommon. However, fainting may become common in patients with heart failure.

In patients with coronary heart disease, an excessive drop in blood pressure may be experienced.

APO LISINOPRIL can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Low Blood Pressure: Dizziness, fainting, light-headedness. May occur when you go from lying or sitting to standing up	√		
Increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell		√	
UNCOMMON			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
Liver and Pancreas Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
RARE			
Anemia (decreased number of red blood cells): fatigue, loss of energy, weakness, shortness of breath.		√	
Decreased Platelets: bruising, bleeding, fatigue and weakness, small purple or red dots under the skin		√	
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
VERY RARE			
Serious Skin Reactions (Stevens- Johnson Syndrome, Toxic Epidermal Necrolysis): any combination of itchy skin, rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
genitals, accompanied by fever, chills, headache, cough, body aches or joint pain.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature 15°C to 30°C.

Do not take your medicine after the expiry date shown on the bottle.

Keep out of reach and sight of children.

If you want more information about APO-LISINOPRIL:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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