



## New Zealand Data Sheet

### APO-LISINOPRIL

#### Lisinopril dihydrate 5mg, 10mg & 20mg Tablets

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#### Presentation

APO-LISINOPRIL 5mg tablets are pink coloured, round biconvex uncoated tablets with “5” debossed on one side and breakline on the other. Each tablet contains lisinopril dihydrate equivalent to anhydrous lisinopril 5mg, and typically weighs 110mg.

APO-LISINOPRIL 10mg tablets are pink coloured, round biconvex uncoated tablets with “10” debossed on one side and breakline on the other. Each tablet contains lisinopril dihydrate equivalent to anhydrous lisinopril 10mg, and typically weighs 220mg.

APO-LISINOPRIL 20mg tablets are pink coloured, round biconvex uncoated tablets with “20” debossed on one side and breakline on the other. Each tablet contains lisinopril dihydrate equivalent to anhydrous lisinopril 20mg, and typically weighs 220mg.

#### Uses

#### Actions

Lisinopril is an angiotensin-converting enzyme (ACE) inhibitor. ACE catalyses the conversion of angiotensin I to the angiotensin II, which is the vasoconstrictor peptide. Inhibition of ACE leads to a decrease in concentration of angiotensin II and results in an increased plasma renin activity and decreased aldosterone secretion. Although the decrease in aldosterone secretion is small it can result in a slight increase of concentration of potassium ions in serum. In patients suffering from hypertension, but with normal renal function, treated with lisinopril and thiazide diuretic no significant change in concentration of potassium in serum occurred. In the group of patients treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1mEq/L; however, 4% of patients had increases greater than 0.5mEq/L and approximately 12% had a decrease greater than 0.5mEq/L.

ACE is identical to kininase, the enzyme that degrades bradykinin. It is not clear if increased levels of bradykinin, a potent vasodepressor peptide, play any significant role in therapeutic effects of lisinopril.

Suppression of the renin – angiotensin – aldosterone system seems to be the primary mechanism through which lisinopril lowers blood pressure. Lisinopril also lowers blood pressure in patients with low renin hypertension.

The antihypertensive effect of lisinopril is generally lower in Afro-Caribbean black patients (usually a low hypertensive population) than in non-blacks. Administering lisinopril and hydrochlorothiazide concomitantly eliminated this difference.

Lisinopril decreases both supine and standing blood pressure in patients with hypertension. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure.

The peak antihypertensive effect of a single dose of lisinopril was usually achieved by 6 hours after dosing with onset at 1-2 hours. The antihypertensive effect could be maintained for up to 24 hours on a single recommended dose but was substantially smaller after 24 hours than 6 hours after administration.

Occasionally, achievement of optional blood pressure reduction may require 2 to 4 weeks of therapy.

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### Pharmacokinetics

Following oral administration of lisinopril, maximum serum concentrations occur within approximately 7 hours. Time to reach peak serum concentration increases to about 8 to 10 hours in patients with recent myocardial infarction. Prolonged terminal phase of declining serum concentrations does not change drug accumulation. Lisinopril binds to ACE serum proteins and does not appear to be bound to other serum proteins. Saturable binding to ACE can probably explain the prolonged terminal phase, which is not proportional to dose.

Lisinopril is not metabolized and is excreted in urine in unchanged form.

Approximately 25% of administered lisinopril is absorbed according to urinary recovery studies, but there is large inter subject variability (6% to 60%) at all doses tested (5-80mg). Presence of food in the gastrointestinal tract does not influence absorption of lisinopril.

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 20mg produced higher serum concentrations than those seen in young healthy adults given a similar dose. In another study 5mg single doses of lisinopril were given to young and elderly healthy volunteers and to elderly subjects with congestive heart failure. The maximum serum concentrations of lisinopril on day 7 of studies were higher in the elderly volunteers than the young, and still higher in the elderly patients with congestive heart failure. Renal clearance of lisinopril was decreased in the elderly particularly with congestive heart failure.

Impaired renal function decreases elimination of lisinopril. This decrease becomes clinically important if the glomerular filtration rate is below 30mL/min. Above this glomerular filtration rate, the elimination half - life is essentially unchanged. With greater impairment however peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged.

Studies in rats indicate that lisinopril crosses the blood – brain barrier poorly. Multiple doses of lisinopril in rats does not result in accumulation in any tissues.

Radioactivity was found to cross the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. Also milk of lactating rats contained radioactivity from C14 labeled lisinopril.

### Indications

- APO-LISINOPRIL is indicated in the treatment of essential hypertension and in renovascular hypertension. It may be used alone or concomitantly with other classes of antihypertensive agents.
- APO- LISINOPRIL is indicated in the management of congestive heart failure as an adjunctive treatment with diuretics and, where appropriate, digitalis.
- APO-LISINOPRIL is indicated for the treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival. Patients should receive, as appropriate, the standard recommended treatment such as thrombolytics, aspirin and betablocker.

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### Dosage and Administration

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

### Essential Hypertension

In patients with essential hypertension the usual recommended starting dose is 10mg. The usual effective maintenance dosage is 20mg administered in a single daily dose. Dosage should be adjusted according to blood pressure response. In some patients, achievement of optimal blood pressure reduction may require two to four weeks of therapy. The maximum dose used in long term, controlled clinical trials was 80mg/day.

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 and may be required in some elderly patients.

### Diuretic Treated Patients

Symptomatic hypotension may occur following initiation of therapy with lisinopril; this is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume- and/or salt-depleted. The diuretic should be discontinued 2 to 3 days before beginning therapy with lisinopril (see Warnings and Precautions). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with lisinopril should be initiated with a 5mg dose. The subsequent dosage of lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

### Dosage Adjustment in Renal Impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1.

TABLE 1

<b>Creatinine Clearance (ml/min)</b>	<b>Starting Dose (mg/day)</b>
< 70 > 30 ml/min	5 mg - 10 mg
< 30 > 10 ml/min	2.5 mg - 5 mg
< 10 ml/min (including patients on dialysis)**	2.5 mg*

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

\*\* See Contraindications

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

### 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. Therefore, a lower starting dose of 2.5 or 5 mg is recommended. Thereafter, the dosage may be adjusted according to the blood pressure response.

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### **Congestive Heart Failure**

As adjunctive therapy with diuretics and where appropriate digitalis lisinopril may be initiated with a dose of 2.5mg once a day. The usual effective dosage range is 5 to 20 mg per day administered in a single daily dose. In clinical trials, dosages were adjusted at 4 week intervals in patients requiring additional therapeutic effect. Dosage adjustments should be based on clinical response of each individual patient.

Patients at high risk of symptomatic hypotension, e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolemia or patients who have been receiving vigorous diuretic therapy, should have these conditions corrected, if possible, prior to therapy with lisinopril. The effect of the starting dosage of lisinopril on blood pressure should be monitored carefully.

### **Acute Myocardial Infarction**

Treatment with lisinopril may be started within 24 hours of the onset of symptoms. 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 (120mm Hg or less) when treatment is started or during the first 3 days after the infarct should be given a lower dose - 2.5 mg orally (see Warnings and Precautions). If hypotension occurs (systolic blood pressure less than or equal to 100mm Hg) 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 90mm Hg for more than 1 hour) PRINIVIL should be withdrawn. Dosing for patients with acute myocardial infarction should continue for six weeks. (For patients who develop symptoms of heart failure, see Dosage and Administration, Congestive Heart Failure).

Lisinopril is compatible with intravenous or transdermal glyceryl trinitrate.

### **Children**

Not recommended for children.

### **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 the dosage should be monitored with particular caution.

### **Contraindications**

APO-LISINOPRIL is contraindicated in cases of hypersensitivity to the product and in patients with a history of angioneurotic oedema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

All ACE inhibitors, including lisinopril, are contraindicated in pregnancy because of the potential risk of fetotoxicity

### **Warnings and Precautions**

#### **Symptomatic Hypotension**

Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving lisinopril hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see Interactions and Adverse Effects). In patients with congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use

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of high doses of loop diuretics, hyponatraemia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patient should be followed closely whenever the dose of APO-LISINOPRIL and/or diuretic is adjusted.

Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with APO-LISINOPRIL. This effect is anticipated and it not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of APO-LISINOPRIL may be necessary.

### **Hypotension in Acute Myocardial Infarction**

Treatment with lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100mm Hg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily 2.5 mg if systolic blood pressure is 100mm Hg or lower. If hypotension persists (systolic blood pressure less than 90mm Hg for more than 1 hour) then APO-LISINOPRIL should be withdrawn.

### **Aortic Stenosis/Hypertrophic Cardiomyopathy**

As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

### **Renal Function Impairment**

In patients with congestive heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases of blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when lisinopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or APO-LISINOPRIL may be required.

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

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### **Hypersensitivity/Angioneurotic Oedema**

Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including lisinopril. This may occur at any time during treatment. In such cases, APO-LISINOPRIL should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient.

Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Very rarely, fatalities have been reported due to angioedema associated with laryngeal edema or tongue edema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy which may include subcutaneous epinephrine solution 1:1000 (0.3ml to 0.5ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-Blacks.

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

### **Anaphylactoid Reactions During Hymenoptera Desensitisation**

Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

### **Haemodialysis Patients**

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g. AN69 Registered TM) and treated concomitantly with an ACE Inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

### **Cough**

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

### **Surgery/Anaesthesia**

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, APO-LISINOPRIL may block 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.

### **Hyperkalaemia**

Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes.

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The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias.

If concomitant use of APO-LISINOPRIL and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium. (See Interactions, *Serum Potassium*).

### **Hypoglycaemia**

Diabetic patients treated with oral anti-diabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycaemia, especially during the first month of combined use. (See Interactions.)

### **Use in the Elderly**

In clinical studies, there was no age-related change in the efficacy or safety profile of lisinopril. When advanced age is associated with decrease in renal function, however, the guidelines set out in Table 1 (see Dosage and Administration, *Dosage Adjustment in Renal Impairment*) should be used to determine the starting dose of APO-LISINOPRIL. Thereafter, the dosage should be adjusted according to the blood pressure response.

### **Use in Pregnancy and Lactation**

Category D

The use of APO-LISINOPRIL during pregnancy is contraindicated. When pregnancy is detected, APO-LISINOPRIL should be discontinued as soon as possible.

ACE inhibitors can cause foetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters.

Use of ACE inhibitors during this period has been associated with foetal and neonatal injury including hypotension, renal failure, hyperkalemia, and/or skull hypoplasia in the newborn. Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

These adverse effects to the embryo and foetus do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester.

Infants whose mothers have taken lisinopril should be closely observed for hypotension, oliguria and hyperkalemia. Lisinopril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

### **Nursing Mothers**

It is not known whether lisinopril is secreted in human milk. Because many medicines are secreted in human milk, caution should be exercised if APO-LISINOPRIL is given to a nursing mother.

### **Paediatric Use**

Safety and effectiveness of lisinopril in children have not been established.

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### **Pancreatitis**

Pancreatitis may occur with angiotensin converting enzyme inhibitors and patients with abdominal pain on ACE inhibitors should be tested accordingly.

### **Animal Toxicity**

The safety of lisinopril has been thoroughly investigated in laboratory animals. The oral LD50 of lisinopril was greater than 20g/kg in mice and rats.

The toxicity of lisinopril in rats and dogs appears to be related principally to an exaggeration of the pharmacologic effects. There was a wide separation between the therapeutic dose in humans and toxic doses in animals.

The ratio of the non-toxic dose in dogs (5mg/kg/day) to a recommended human dose of 40mg/day was greater than 6 in this sensitive species.

With a dose of 40mg/day in humans, the maximum plasma lisinopril concentration was 468ng/ml, well below the 11,370ng/ml plasma level produced by a nephrotoxic dose in dogs.

The principal signs of toxicity in dogs were related to changes in renal function (elevated serum urea nitrogen and creatinine concentrations), sometimes associated with renal tubular degeneration. This last change was not observed in rats, but increases in serum urea nitrogen were recorded.

The changes in renal function probably represent a medicine-induced pre-renal azotemia related to the pharmacologic activity of lisinopril. Saline-supplementation ameliorated or prevented the toxicity of lisinopril in rats as well as dogs, further substantiating a mechanism-based toxicity.

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90mg/kg/day (about 110 times the maximum recommended daily human dose).

Lisinopril has also been administered for 92 weeks to (male and female) mice at doses up to 135mg/kg/day (about 170 times the maximum recommended daily human dose) and showed no evidence of carcinogenicity.

Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow.

There were no adverse effects on reproductive performance in male and female rats treated with up to 300mg/kg/day of lisinopril.

Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1000mg/kg/day (1250 times the maximum recommended human dose). There was an increase in foetal resorptions at doses down to 100mg/kg; at doses of 1000mg/kg this was prevented by saline supplementation. There was no foetotoxicity or teratogenicity in rats treated with up to 300mg/kg/day (375 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 of pup deaths on days 2-7 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.

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Lisinopril at doses up to 1mg/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 materno- and foetotoxic effects apparent at or below the recommended therapeutic dosage levels in humans.

Foetotoxicity was demonstrated in rabbits by an increased incidence of foetal resorptions at an oral dose of lisinopril of 1mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1mg/kg/day). A single intravenous dose of 15mg/kg/day of lisinopril administered to pregnant rabbits during gestation days 16, 21 or 26 resulted in 88% to 100% foetal death.

### Adverse Effects

Lisinopril has been found in controlled clinical trials to be generally well tolerated. For the most part, adverse reactions were mild and transient in nature.

In clinical trials in patients with hypertension treated with Lisinopril, discontinuation of therapy due to clinical adverse experiences occurred in 5.7% of patients.

#### Heart failure

Lisinopril therapy has been discontinued due to clinical adverse effects occurred in 11.0 percent of patients with heart failure treated for up to four years. In controlled studies in patients with heart failure, therapy was discontinued in 8.1% of patients treated with Lisinopril for up to 12 weeks, compared to 7.7% of patients treated with placebo for up to 12 weeks.

The following table list, those adverse experiences which occurred in greater than one percent of patients with heart failure treated with Lisinopril or placebo for up to 12 weeks in controlled clinical trials and more frequently on Lisinopril than placebo.

	Controlled trials	
	Lisinopril (n=407)	Placebo (n=155)
	Incidence (discontinuation) 12 weeks	Incidence (discontinuation) 12 weeks
<b>Body as a whole</b>		
Chest pain	3.4 (0.2)	1.3 (0.0)
Abdominal pain	2.2 (0.7)	1.9 (0.0)
<b>Cardiovascular</b>		
Hypertension	4.4 (1.7)	0.6 (0.6)
<b>Digestive</b>		
Diarrhea	3.7 (0.5)	1.9 (0.0)
<b>Nervous/Psychiatric</b>		
Dizziness	11.8 (1.2)	4.5 (1.3)
Headache	4.4 (0.2)	3.9 (0.0)
<b>Respiratory</b>		
Upper respiratory infection	1.5 (0.0)	1.3 (0.0)
<b>Skin</b>		
Rash	1.7 (0.5)	0.6 (0.6)

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### **Acute Myocardial Infarction**

In the trial patients treated with Lisinopril for six weeks following acute myocardial infarction, discontinuation of therapy occurred in 17.6 % of patients.

The most frequent clinical side effects of Lisinopril in controlled trials were: dizziness, headache, diarrhea, fatigue, cough and nausea.

Other side effects, which are less frequent, were orthostatic effects (more frequent if Lisinopril therapy is combined with Hydrochlorothiazide) (including hypotension), rash, and asthenia.

Hypersensitivity - Angioneurotic Oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (Warnings and Precautions).

Other side effects that occurred usually in less than 2% of patients in controlled studies include:

**Cardiovascular:** Cardiac arrest, myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see Precautions), palpitations, tachycardia, pulmonary embolism and infarction, arrhythmias (including ventricular tachycardia, atrial tachycardia, atrial fibrillation, bradycardia and premature ventricular contractions)

**Digestive:** abdominal pain and indigestion, dry mouth, hepatitis - either hepatocellular or cholestatic, jaundice, pancreatitis (see Warnings and Precautions), gastritis, dyspepsia, vomiting

**Nervous System:** mood alterations, mental confusion, paresthesia, vertigo, taste disturbances and sleep disturbances have been reported.

**Respiratory:** bronchospasm, rhinitis, sinusitis

**Skin:** alopecia, diaphoresis, pruritus, urticaria, psoriasis and severe skin disorders such as pemphigus, toxic epidermal necrolysis, Stevens - Johnson syndrome and erythema multiforme have been reported.

**Urogenital:** impotence, oliguria/anuria, renal dysfunction, acute renal failure.

### **Clinical Laboratory Test Findings:**

**Serum electrolytes:** Hyperkalemia, hyponatremia.

**Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0 percent of patients with essential hypertension treated with Lisinopril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 11.6 percent of patients with heart failure on concomitant diuretic therapy. Usually with decrease of diuretic dosage abnormalities resolved.

**Haemoglobin and Hematocrit:** small decreases in haemoglobin and hematocrit occurred frequently in patients treated with Lisinopril. Haemolytic anaemia has been reported; a causal relationship to Lisinopril cannot be excluded.

**Liver function tests:** rarely, increases of liver enzymes and /or serum bilirubin have occurred. (See warnings: Hepatic failure).

Elevations in blood urea nitrogen, serum creatinine, and serum potassium have been reported in hypertensive patients undergoing Lisinopril therapy. In the myocardial infarction trial 2.0 percent of the patients receiving Lisinopril therapy discontinued treatment due to renal dysfunction.



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The following additional events have been reported but a casual relationship to therapy with Lisinopril cannot be excluded:

**Body as a whole:** chest pain, flushing, syncope.

**Cardiovascular system:** angina pectoris, rhythm disturbances.

**Digestive System:** anorexia, constipation, dyspepsia, flatulence, vomiting.

**Metabolic:** gout

**Musculoskeletal system:** back pain, joint pain muscle cramps, shoulder pain.

**Nervous systems and psychiatric:** decreased libido, depression, insomnia, somnolence, stroke, and vertigo.

**Respiratory system:** bronchitis, dyspnoea, nasal congestion, pharyngeal pain, sinusitis, and upper respiratory symptoms.

**Urogenital:** urinary tract infection

**Other:** blurred vision, rare cases of neutropenia and bone marrow depression.

### Interactions

#### Diuretics:

When a diuretic is administered during lisinopril therapy, the antihypertensive effect is usually additive.

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. That can be prevented or risk minimized by discontinuing the diuretic prior to initiation of treatment with lisinopril and/ or lowering the initial dose of lisinopril.

#### Other Agents

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory medicines including selective cyclooxygenase-2 inhibitors, the co-administration of ACE inhibitors may result in a further deterioration of renal function. These effects are usually reversible.

Lisinopril has been used concomitantly with nitrates without evidence of clinically significant adverse interactions.

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

#### Serum Potassium:

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalemia did occur in some cases.



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Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride) or potassium supplements or potassium-containing salt substitutes).

The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If concomitant use of APO-LISINOPRIL and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium. If APO-LISINOPRIL is given with a potassium-losing diuretic diuretic-induced hypokalaemia may be ameliorated. (See Warnings and Precautions, *Hyperkalaemia*.)

### Anti-diabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and anti-diabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral anti-diabetic agents or insulin, glycaemic control should be closely monitored for hypoglycaemia, especially during the first month of treatment with an ACE inhibitor.

### Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including lisinopril.

### Overdosage

Overdose symptoms include severe hypotension, electrolyte disturbances, and renal failure. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs, patient should be placed in the shock position and intravenous saline solution should be infused immediately. Vasopressors including angiotensin II may be administered if fluid replacement is inadequate or contraindicated. Lisinopril serum concentration can be decreased by hemodialysis. High-flux polyacrylonitrile dialysis membranes should be avoided (see Precautions – anaphylactoid reactions during membrane exposure). Serum electrolytes and creatinine should be monitored frequently.

### Pharmaceutical Precautions

Store at or below 25°C. Protect from heat, light and moisture.  
Shelf life 3 years

### Medicine Classification

Prescription Medicine

### Package Quantities

5mg: Blister packs containing 28 tablets.  
10mg: Blister packs containing 28 tablets  
20mg: Blister packs containing 28 tablets

### Further Information

Nil



## APO-LISINOPRIL

Lisinopril dihydrate 5mg, 10mg & 20mg Tablets

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### **Date of Preparation**

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