

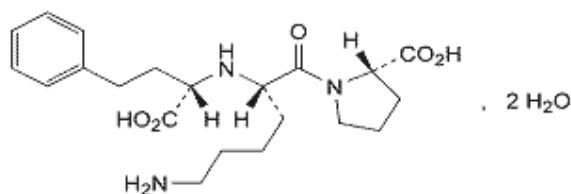
# Arrow - Lisinopril

Lisinopril tablets

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## Name of the drug

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Lisinopril dihydrate. The chemical name for lisinopril dihydrate is N-[N-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate. Its structural formula is:

C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>O<sub>5</sub>·2H<sub>2</sub>O Molecular weight: 441.53 CAS No.: 83915-83-7

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## Description

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

Arrow - Lisinopril tablets come in three strengths and contain lisinopril dihydrate equivalent to 5 mg, 10 mg or 20 mg of lisinopril. The tablets also contain the following excipients: mannitol, calcium hydrogen phosphate, maize starch, pregelatinised maize starch, colloidal anhydrous silica and magnesium stearate. The tablets are gluten free.

A synthetic peptide derivative, lisinopril dihydrate is an oral long acting angiotensin converting enzyme inhibitor. It is a lysine analogue of enalaprilat (active metabolite of enalapril).

### **Pharmacology**

#### **Pharmacological Actions**

Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of plasma angiotensin II which results in decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with lisinopril alone for up to 24 weeks, the mean increase in serum potassium was approximately 0.1 mmol/L; however, approximately 15% of patients had increases greater than 0.5 mmol/L and approximately 6% had a decrease greater than 0.5 mmol/L. In the same study, patients treated with lisinopril and hydrochlorothiazide for up to 24 weeks had a mean decrease in serum potassium of 0.1 mmol/L;

approximately 4% of patients had increases greater than 0.5 mmol/L and approximately 12% had a decrease greater than 0.5 mmol/L (see PRECAUTIONS). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system (RAAS), lisinopril is antihypertensive even in patients with low renin hypertension. Although lisinopril was antihypertensive in all races studied, black hypertensive patients (usually a low renin hypertensive population) had a smaller average response to monotherapy than non-black patients. Concomitant administration of lisinopril and hydrochlorothiazide further reduced blood pressure in black and non-black patients and any racial difference in blood pressure response was no longer evident.

ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated. When combined with other antihypertensive agents, additive falls in blood pressure may occur.

ACE is known to be present in the endothelium and increased ACE activity in diabetic patients which results in the formation of angiotensin II and destruction of bradykinin, potentiates the damage to the endothelium caused by hyperglycaemia. ACE inhibitors, including lisinopril, inhibit the formation of angiotensin II and breakdown of bradykinin and hence ameliorate endothelial dysfunction.

The effects of lisinopril on urinary albumin excretion rate and on the progression of retinopathy in diabetic patients is mediated by a reduction in blood pressure as well as a direct mechanism on the renal and retinal tissues. Lisinopril treatment is not associated with an increased incidence of hypoglycaemic events in diabetic patients and it does not affect glycaemic control as shown by a lack of significant effect on levels of glycosylated haemoglobin (HbA1c).

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## **Clinical trials**

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### ***Acute myocardial infarction.***

Lisinopril is indicated in the management of patients with acute myocardial infarction to prevent the subsequent development of left ventricular dysfunction (as defined by an ejection fraction less than or equal to 35%) or heart failure and to improve survival, based on the outcome of the Gruppo Italiano per lo Studio della Sporavvenienza nell'Infarto Miocardico (GISSI-3) trial. The GISSI-3 study was a multicentre, controlled, randomised, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction admitted to a coronary care unit. It was designed to examine the effects of short-term (six week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (six week) mortality and on longer-term death and markedly impaired cardiac function. Patients presenting within 24 hours of the onset of symptoms who were haemodynamically stable were randomised, in a

2 x 2 factorial design, to six weeks of either lisinopril alone (n = 4,841), nitrates alone (n = 4,869), lisinopril plus nitrates (n = 4,841) or open control (n = 4,843). All patients received routine therapies, including thrombolytics (72%), aspirin (84%) and a beta-blocker (31%), as appropriate, normally utilised in acute myocardial infarction (MI) patients.

The protocol excluded patients with hypotension (systolic blood pressure less than or equal to 100 mmHg), severe heart failure, cardiogenic shock, and renal dysfunction (serum creatinine > 2 mg/dL and/or proteinuria > 500 mg/24 hours). Doses of lisinopril were adjusted as necessary according to protocol (see Dosage and Administration).

Study treatment was withdrawn at six weeks except where clinical conditions indicated continuation of treatment.

The primary outcomes of the trial were the overall mortality at six weeks and a combined endpoint at six months after the myocardial infarction, consisting of a number of patients who died, had late (day 4) clinical congestive heart failure, or had extensive left ventricular damage defined as ejection fraction less than or equal to 35% or an akinetic-dyskinetic (A-D) score greater than or equal to 45%. Patients receiving lisinopril (n = 9,646), alone or with nitrates, had an 11% lower risk of death at six weeks (2p (two tailed) = 0.04) compared to patients receiving no lisinopril (n = 9,672) (6.4 versus 7.2%, respectively). The reduction in mortality at six months was not significant, but this was not a primary outcome measure. Although patients randomised to receive lisinopril for up to six weeks also fared numerically better on the combined endpoint at six months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of lisinopril between six weeks and six months in the group randomised to six weeks of lisinopril, preclude any conclusion about this endpoint.

Patients with acute myocardial infarction treated with lisinopril had a higher (9.0 versus 3.7%) incidence of persistent hypotension (systolic blood pressure < 90 mmHg for more than one hour) and renal dysfunction (2.4 versus 1.1%) in hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration).

### ***Renal complication of diabetes.***

EUCLID (EURODIAB controlled trial of lisinopril in insulin dependent diabetes mellitus) was an 18 centre, multinational, randomised, double blind, placebo controlled trial. It investigated the effects of lisinopril on the urinary albumin excretion rate (AER) in 530 normotensive men and women aged 20 to 59 years with insulin dependent diabetes mellitus (IDDM) and normoalbuminuria or microalbuminuria. The study recruited patients with a diastolic blood pressure in the range of 75 to 90 mmHg inclusive provided that the systolic blood pressure was less than or equal to 155 mmHg. Patients received either lisinopril 10 mg once daily or matching placebo for two years. Titration up to 20 mg once daily of lisinopril or two placebo tablets was permitted if sitting diastolic blood pressure had not reached the target value of less than 75 mmHg after three months of treatment. Nifedipine treatment (20 mg twice

daily) was initiated if the blood pressure remained inadequately controlled (systolic blood pressure > 160 mmHg, diastolic blood pressure > 95 mmHg).

The primary efficacy variable was the rate of change in the urinary albumin excretion rate (AER) measured from two consecutive overnight urine collections at six monthly intervals from baseline to 24 months in the whole patient group (i.e. normoalbuminuric and microalbuminuric at baseline). After 24 months treatment the AER was 18.8% (95% CI: 2.0, 32.7) lower in the lisinopril group (n = 230) compared to the placebo group (n = 226) with a between group difference of 2.2 microgram/minute (p = 0.03) when adjusted for baseline AER and centre. After adjustment for diastolic blood pressure reduction produced by lisinopril, the between group relative difference in AER was reduced to 17.3% (95% CI: 0.2, 31.5, p = 0.05). There were no statistically significant differences in AER between lisinopril and placebo in patients with good baseline glycaemic control (HbA1C < 7%) or with a baseline diastolic blood pressure > 80 mmHg.

In patients with baseline microalbuminuria the AER was 49.7% (95% CI: 14.5, 77.9) lower in the lisinopril group (n = 39) compared to placebo (n = 34), p = 0.1. Only 15% (n = 79) of the randomised patients had baseline microalbuminuria compared to 40% anticipated by the protocol. This may have left the study underpowered to detect a statistically significant difference in the AER between treatments in patients with baseline microalbuminuria. In a nonprotocol specified subgroup analysis in patients with baseline microalbuminuria (AER 20 to 200 microgram/minute) and endpoint AER the absolute difference in mean AER between the lisinopril group (n = 39) and the placebo group (n = 34) was 38.5 microgram/minute (p = 0.001).

The results also show that lisinopril does not increase the risk of hypoglycaemic events in IDDM as there was no treatment difference in hypoglycaemic events or glycaemic control throughout the study.

### ***Congestive heart failure.***

The effect of lisinopril on mortality in congestive heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). Patients receiving high dose lisinopril were titrated gradually up to the highest dose tolerated, up to a maximum of 32.5 mg or 35 mg once daily. Patients who were intolerant to lisinopril were excluded from the study. In a study of 3,164 patients, with a median follow up period of 46 months for surviving patients, statistically nonsignificant reductions were observed in the primary endpoint of all cause mortality or the secondary endpoint of cardiovascular mortality. However, compared with low dose, high dose lisinopril produced a 12% risk reduction in the combined endpoint of all cause mortality and all cause hospitalisation (p = 0.002), an endpoint added during the trial. In a post hoc analysis, the number of hospitalisations for heart failure was reduced by 24% (p = 0.002) in patients treated with high dose lisinopril compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of lisinopril. This trial did not study whether 35 mg is more effective than the currently recommended upper limit of the usual dose of 20 mg.

The results of the study showed that the overall adverse event profiles for patients treated with high or low dose lisinopril were similar in both nature and number. The overall adverse event rate included deaths and hospitalisations that contributed to the estimation of efficacy. The percentage of drug related adverse events was 8% higher in the high dose group (a relative difference of 25%). The excess in the high dose group was due to events of the type which would be expected from the pharmacological actions of lisinopril. Predictable events resulting from ACE inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose lisinopril compared with low dose. New York Heart Association classification (a measure of quality of life) did not differ between treatment groups.

### ***Pharmacokinetics***

Following oral administration of lisinopril, peak serum concentrations of lisinopril occur within about seven hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. Declining serum concentrations exhibit a prolonged terminal phase, which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not appear to be bound to other serum proteins.

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with large interpatient variability (6 to 60%) at all doses tested (5 to 80 mg). Lisinopril absorption is not affected by the presence of food in the gastrointestinal tract.

Upon multiple dosing, lisinopril exhibits an effective half-life of accumulation of 12.6 hours.

Impaired renal function decreases elimination of lisinopril, which is excreted principally through the kidneys, but this decrease, becomes clinically important only when the glomerular filtration rate (GFR) is below 30 mL/minute. Above this GFR, the elimination half-life is little changed. With greater impairment, however, peak and trough lisinopril levels increase, time to peak concentration increases and time to attain steady state is prolonged. Older patients, on average, have higher (approximately doubled) blood levels and higher values for the area under the plasma concentration time curve (AUC) than younger patients. (See DOSAGE AND ADMINISTRATION) Lisinopril can be removed by haemodialysis.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Multiple doses of lisinopril in rats do not result in accumulation in any tissues. Milk of lactating rats contained radioactivity following administration of <sup>14</sup>C lisinopril. By whole body autoradiography, radioactivity was found in the placenta following administration of labelled drug to pregnant rats, but none was found in the fetuses.

### ***Pharmacodynamics***

Administration of lisinopril to patients with hypertension results in a reduction of supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is usually not observed although it can occur and should be anticipated in volume and/or salt depleted patients (see PRECAUTIONS). When given together with thiazide-type diuretics, the blood pressure lowering effects of the two drugs are approximately additive.

In most patients studied, onset of antihypertensive activity was seen one to two hours after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by six hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses.

However, in all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was six hours after dosing.

In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy. The antihypertensive effects of lisinopril are maintained during long-term therapy. Abrupt withdrawal of lisinopril has not been associated with a rapid increase in blood pressure or a significant increase in blood pressure compared to pretreatment levels.

Two dose-response studies utilising a once daily regimen were conducted in 438 mild to moderately hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of lisinopril was seen with 5 mg in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with lisinopril 10, 20, or 80 mg. In controlled clinical studies, lisinopril 20 to 80 mg has been compared in-patients with mild to moderate hypertension with hydrochlorothiazide 12.5 to 50 mg and with atenolol 50 to 200 mg, and in patients with moderate to severe hypertension with metoprolol 100 to 200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic blood pressure in a population that was three-quarters Caucasian. Lisinopril was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure and had somewhat greater effects on systolic blood pressure.

Lisinopril had similar effectiveness and adverse effects in younger and older (> 65 years) patients. It was less effective in the black population than in the Caucasian population.

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

GFR in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

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## Indications

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- 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.
- Lisinopril is indicated in the management of congestive heart failure as an adjunctive treatment with diuretics and, where appropriate, digitalis.
- 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 treatments such as thrombolytics, aspirin and beta-blocker.

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## Contraindications

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- Hypersensitivity to lisinopril or any other component of lisinopril.
- History of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor.
- Patients with hereditary or idiopathic angioedema.
- Pregnancy (see PRECAUTIONS, Use in pregnancy).
- Patients undergoing haemodialysis with polyacrylonitrile metalylsulfonate high flux membranes. There is a risk of anaphylactoid reaction (hypersensitivity reactions which may be severe, e.g. shock) with the simultaneous use of an ACE inhibitor and polyacrylonitrile metalylsulfonate high flux dialysis membranes (e.g. AN69) or during low-density lipoproteins (LDL) apheresis with dextran sulphate within the framework of dialysis treatment. This combination thus needs to be avoided, either by using other medical products to control high blood pressure or cardiac insufficiency or by using other membranes during dialysis.

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## Warnings and Precautions

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### **Dual blockade of the renin-angiotensin-aldosterone system**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

**Hyperkalaemia:** Because the ACE inhibitors decrease the formation of angiotensin II and the subsequent production of aldosterone, serum

potassium concentrations exceeding 5.5 mEq/L may occur. Hyperkalaemia is more likely in-patients with some degree of renal impairment, those treated with potassium sparing diuretics or potassium supplements, and in those consuming potassium containing salt substitutes. Diabetic patients, and elderly diabetic patients particularly, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may coexist with hyperkalaemia. It is recommended that patients taking an ACE inhibitor should have serum electrolytes (including potassium, sodium and urea) measured from time to time. This is more important in-patients taking diuretics.

**Surgery and anaesthesia:** In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. If perioperative hypotension occurs, volume expansion would be required.

**Cough:** A persistent dry (nonproductive) irritating cough has been reported with ACE inhibitors. In various studies, the incidence of cough varies depending on the drug, dosage, duration of use and method of analysis. The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins, which accumulate because of ACE inhibition. A change to another class of drugs may be required in severe cases.

**Dermatological reactions:** Dermatological reactions characterised by maculopapular pruritic rashes and sometimes photosensitivities have been reported rarely with ACE inhibitors. Rare and occasionally severe skin reactions (e.g. lichenoid eruptions, psoriasis, pemphigus-like rash, Stevens-Johnson syndrome) have also been reported with some ACE inhibitors. A causal relationship is sometimes difficult to assess. Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross reactivity.

**Taste disturbances (dysgeusia):** The incidence of taste disturbance was reported to be high (up to 12.5%) with high doses of another ACE inhibitor but the overall incidence for the class is probably low. However, the relevant data are scarce and difficult to interpret. The taste disturbance has been described as a suppression of taste or a metallic sensation in the mouth. The dysgeusia usually occurs in the first few weeks of treatment and may disappear within one to three months despite continued treatment.

**Impaired renal function:** 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 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 lisinopril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of lisinopril.

**Impaired hepatic function:** Hepatitis (hepatocellular and/or cholestatic) and elevations of hepatic enzymes and/or serum bilirubin have occurred during therapy with other ACE inhibitors in patients with or without pre-existing hepatic abnormalities. In most cases the changes were reversed on discontinuation of the drug. There are no adequate studies in patients with cirrhosis and/or hepatic dysfunction. Lisinopril should be used with particular caution in patients with pre-existing hepatic 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.

**Anaphylactoid reactions during Hymenoptera desensitisation:** Patients receiving ACE inhibitors during desensitisation (e.g. Hymenoptera venom) have experienced anaphylactoid reactions. These reactions have been avoided when ACE inhibitors were temporarily withheld.

**Angioedema:** Severe life-threatening angioedema has been reported rarely with most of the ACE inhibitors. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. Most commonly, angioedema occurs during the first week of therapy but it has also been reported after long-term therapy. Patients may have multiple episodes of angioedema with long symptom free intervals.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors. This may occur at any time during treatment. In such cases lisinopril should be discontinued promptly; appropriate monitoring instituted to ensure complete resolution of symptoms prior to the patient being dismissed. Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon. In instances where swelling has been confined to the face and lips, the angioedema has generally resolved without treatment or with antihistamines. Angioedema associated with laryngeal oedema is potentially life threatening. Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Where involvement of

the tongue, glottis or larynx is likely to cause airway obstruction, appropriate emergency therapy, including adrenaline and oxygen administration, and/or the maintenance of a patent airway, should be carried out promptly and the patient may need to be hospitalised. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. Angioedema may occur with or without urticaria.

Race: ACE inhibitors cause a higher rate of angioedema in Afro-Caribbean black patients than in non-Afro-Caribbean black patients. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema whilst receiving an ACE inhibitor.

**Symptomatic hypotension:** Hypotension may occur in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in patients with uncomplicated hypertension but can develop in patients with impaired renal function, in those who are salt or volume depleted because of renovascular disease, diuretic therapy, vomiting or diarrhoea, and in patients undergoing dialysis. (See PRECAUTIONS, Interactions with other drugs and ADVERSE REACTIONS.) In patients with severe congestive cardiac failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with syncope, neurological deficits, oliguria and/or progressive azotaemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased or diuretic therapy is commenced or increased.

Similar considerations may 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, respectively. In all high-risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty once the blood pressure, has increased. As with other vasodilators, lisinopril should be given with caution to patients with aortic stenosis or hypertrophic cardiomyopathy.

**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, i.e. patients with a systolic blood pressure of 100 mmHg or lower or cardiogenic shock. During the first three days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mmHg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mmHg or lower. If hypotension persists (systolic blood pressure < 90 mmHg for more than one hour), lisinopril should be withdrawn.

**Neutropenia/agranulocytosis:** Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression (including leucopenia and neutropenia). These reports generally involve patients who have pre-existing renal dysfunction and/or collagen vascular disease, some of whom have received concomitant immunosuppressant therapy. Most reports describe transient episodes for which a causal relationship to the ACE inhibitor could not be established. Available data from clinical trials of lisinopril are insufficient to show that lisinopril does not cause agranulocytosis at similar rates. International marketing experience has revealed cases of neutropenia or agranulocytosis in which a causal relationship to lisinopril cannot be excluded.

It is recommended that periodic haematological monitoring be considered in patients with diseases known to affect bone marrow function (e.g. renal dysfunction, collagen vascular disease) and/or who are taking concomitant therapy known to be associated with bone marrow depression.

**Diabetic patients:** In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with lisinopril.

#### ***Carcinogenesis, mutagenesis, impairment of fertility***

There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day or when lisinopril was administered for 92 weeks to male and female mice at doses up to 135 mg/kg/day. At least one other ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential for lisinopril to cause a similar effect is unknown. Lisinopril was not genotoxic in assays for gene mutations, chromosomal damage and DNA damage.

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

#### ***Use in pregnancy (Category D)***

ACE inhibitors should not be used in pregnancy. When pregnancy is detected the ACE inhibitor should be discontinued as soon as possible, unless it is considered life saving for the mother.

There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but fetotoxicity is well-documented in animal models. However, data show that ACE inhibitors cross the human placenta. Postmarketing experience with all ACE inhibitors suggests that exposure in utero may be associated with hypotension and decreased renal perfusion in the fetus. ACE inhibitors have also been associated with fetal death in utero. Adverse effects appear to be most likely in the second and third trimesters.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of fetal hypotension, renal failure,

hyperkalaemia, skull hypoplasia and death. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

Oligohydramnios has been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, however it is not clear whether these events were due to ACE inhibitor exposure.

Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion. Lisinopril has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit and theoretically may be removed by exchange transfusion.

***Use in lactation.***

Milk of lactating rats contains radioactivity following administration of <sup>14</sup>C lisinopril. It is not known whether this drug is secreted in human milk. Because the possibility exists that lisinopril may be secreted in human milk, lisinopril should not be given to a breastfeeding mother.

***Use in children.***

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

***Effect on ability to drive or operate machinery.***

When driving vehicles or operating machines, patients may experience dizziness or tiredness.

***Instructions to patients.***

**Angioedema:** Angioedema, including laryngeal oedema, may occur at any time during treatment with lisinopril. While this condition is rare, patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips or tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing doctor.

**Symptomatic hypotension:** Patients should be cautioned to report light-headedness, especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing doctor. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, e.g. vomiting or diarrhoea, may also lead to a fall in blood pressure; patients should be advised to consult with their doctor.

**Hyperkalaemia:** Patients should be told not to use salt substitutes containing potassium without consulting their doctor.

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

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

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## Interactions

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**Diuretics:** When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. If it is not possible to discontinue the diuretic, the starting dose of the ACE inhibitor should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised.

**Lithium:** Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

**Nonsteroidal anti-inflammatory drugs:** Drugs with prostaglandin synthetase inhibitory properties (e.g. indomethacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors. In some patients with compromised renal function who are being treated with nonsteroidal anti-inflammatory drugs (NSAIDs), the co-administration of lisinopril may result in a further deterioration in renal function.

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

**Agents affecting sympathetic activity:** Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neuron blocking agents) may be used with caution. Beta-Adrenergic blocking drugs are also antihypertensive in action, hence if they are combined with an ACE inhibitor the patient should be closely monitored.

**Serum potassium:** ACE inhibitors can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. The concomitant therapy of an ACE inhibitor with a potassium sparing diuretic (e.g. spironolactone, triamterene or amiloride), potassium supplement or

potassium containing salt substitute can increase the risk of hyperkalaemia. Therefore, if coadministration is indicated these agents should be used with caution and the patient's serum potassium should be monitored frequently.

**Other antihypertensive agents:** When combined with other antihypertensive agents, additive falls in blood pressure may occur.

**Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics:** The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

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

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## Adverse Reactions

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Lisinopril has been found to be generally well tolerated in controlled clinical trials. For the most part, adverse experiences were mild and transient in nature. In patients with congestive heart failure high doses of lisinopril may predispose to symptoms related to hypotension (dizziness, syncope) and biochemical changes related to impaired renal function (hyperkalaemia and increased serum creatinine), as would be expected with ACE inhibitor therapy.

The adverse events that occurred in controlled clinical trials with lisinopril are taken from the case reports of 3,702 patients (2,633 patients with hypertension and 636 patients with congestive cardiac failure and 433 diabetic patients).

**Hypertension.** Adverse reactions reported in 2,633 patients with hypertension follow.

### **More common reactions (3 to 10%)**

Nervous system. Dizziness, headache.

### **Less common reactions (1 to 3%)**

Body as a whole. Asthenia/ fatigue.

Cardiovascular. Chest pain.

Gastrointestinal. Diarrhoea, nausea, vomiting.

Respiratory. Cough.

Dermatological. Rash.

**Rare reactions (< 1%)**

Cardiovascular Hypotension, orthostatic effects, angina, oedema, palpitation, rhythm disturbances.

Gastrointestinal Dyspepsia, anorexia, constipation, flatulence.

Nervous system. Paraesthesia, depression, somnolence, insomnia, vertigo.

Respiratory. Dyspnoea, orthopnoea.

Dermatological. Pruritus.

Musculoskeletal. Muscle cramps, back pain, leg pain, shoulder pain.

Other. Blurred vision, fever, flushing, gout, decreased libido, malaise.

Congestive cardiac failure. Adverse reactions reported in 636 patients with congestive cardiac failure. The most common adverse reaction occurring in this patient population was dizziness (14.2%). The other adverse reactions follow.

**More common reactions (3 to 10%)**

Nervous system. Headache.

Cardiovascular. Hypotension, chest pain, angina.

Gastrointestinal. Diarrhoea, nausea.

Respiratory. Cough, dyspnoea.

Dermatological. Rash.

Body as a whole. Asthenia/ fatigue.

**Less common reactions (1 to 3%)**

Cardiovascular. Orthostatic effects, oedema, palpitation.

Gastrointestinal. Vomiting, dyspepsia, anorexia.

Nervous system. Paraesthesia, depression, insomnia.

Dermatological. Pruritus.

Musculoskeletal. Muscle cramps, back pain, leg pain.

Other. Blurred vision, fever, gout, malaise.

**Rare reactions (< 1%)**

Cardiovascular. Rhythm disturbances.

Gastrointestinal. Constipation, flatulence.

Nervous system. Somnolence, vertigo.

Respiratory. Orthopnoea.

Musculoskeletal. Shoulder pain.

Other. Flushing decreased libido.

**Renal and retinal complications of diabetes mellitus.** Adverse events from two clinical trials in diabetic patients (433 patients receiving lisinopril) are as follows. (The adverse events from each trial that were reported by < 1% of the patients are not included.)

**More common reactions (3 to 10%)**

Body as a whole. Abdominal pain, flu syndrome.

Nervous system. Dizziness.

Respiratory. Bronchitis increased cough, pharyngitis.

**Less common reactions (1 to 3%)**

Body as a whole. Accidental injury, asthenia, back pain, chest pain, fever, headache, infection, pain.

Cardiovascular. Tachycardia.

Gastrointestinal. Diarrhoea, dyspepsia, gastroenteritis, nausea.

Metabolic. Hyperglycaemia, hypoglycaemia.

Musculoskeletal. Arthritis, myalgia.

Nervous system. Vertigo.

Respiratory. Dyspnoea, rhinitis, sinusitis, otitis media.

Dermatological. Rash.

Genitourinary. Cystitis, impotence, urinary tract infection.

**Rare reactions (< 1%)**

Body as a whole. Generalised oedema, neck pain, pelvic pain.

Cardiovascular. Angina pectoris, cerebral ischaemia, hypertension, palpitations.

Gastrointestinal. Constipation, flatulence, gastritis, vomiting.

Dermatological. Eczema.

Metabolic. Hyperlipidaemia, hypoglycaemic reaction, peripheral oedema.

Musculoskeletal. Arthrosis, bursitis, pathological fracture, tendon disorder.

Nervous system. Anxiety, depression, hypertonia, paraesthesia.

Special senses. Ear disorder, taste perversion.

Genitourinary. Dysuria, haematuria, kidney pain.

### **General.**

Hypersensitivity/ angioneurotic oedema. Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (see PRECAUTIONS). In very rare cases, intestinal angioedema has been reported.

Additional adverse reactions, which occurred rarely, either during, controlled clinical trials or after the drug was marketed, include the following:

Cardiovascular. Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS); tachycardia.

Gastrointestinal. Abdominal pain, dry mouth, hepatitis (hepatocellular and cholestatic, very rarely this may progress to hepatic failure), jaundice, pancreatitis, taste disturbance.

Musculoskeletal. Joint pain.

Nervous system. Mood alterations, mental confusion, stroke, sleep disturbances.

Respiratory. Bronchitis, bronchospasm, nasal congestion, pharyngeal pain, sinusitis, rhinitis.

Dermatological. Alopecia, urticaria, diaphoresis, psoriasis and severe skin disorders have been reported, including pemphigus, toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme.

Genitourinary. Uraemia, oliguria/ anuria, proteinuria, renal dysfunction, acute renal failure, impotence, urinary tract infection.

Body as a whole. Syncope.

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/ arthritis, a positive antinuclear antibody (ANA) test, an elevated erythrocyte sedimentation rate (ESR), eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

### **Clinical laboratory test findings.**

Serum electrolytes: Hyperkalaemia (see PRECAUTIONS) and hyponatraemia have occurred.

Creatinine, blood urea nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in 1.1 and 1.6% of patients, respectively, with essential hypertension treated with lisinopril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see PRECAUTIONS). Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 12% of patients with congestive cardiac failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.

Bone marrow depression: Bone marrow depression, manifest as anaemia, and/or thrombocytopenia and/or leucopenia has been reported. Agranulocytosis has been rarely reported, although a causal relationship has not been established. Rarely, haemolytic anaemia has been reported.

Haemoglobin and haematocrit: Small decreases in haemoglobin and haematocrit, rarely of clinical importance unless another cause of anaemia coexisted, have occurred.

Other (causal relationship unknown): Rarely, elevations of hepatic enzymes and/or serum bilirubin have occurred. Rare cases of bone marrow depression have been reported. Thrombocytopenia and leucopenia have been reported; a causal relationship to therapy with lisinopril cannot be excluded.

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## **Dosage and Administration**

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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 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.

### **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 PRINIVIL 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.

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## **Overdosage**

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There are no data on overdosage in humans. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. Lisinopril may be removed from the general circulation by haemodialysis.

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## **Presentation**

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**Arrow - Lisinopril 5**, White, round tablet, marked L | 5 on one side and > on the other side; blister packs of 30.

**Arrow - Lisinopril 10**, White, round tablet, marked L | 10 on one side and > on the other side; blister packs of 30.

**Arrow - Lisinopril 20**, White, round tablet, marked L | 20 on one side and > on the other side; blister packs of 30.

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## **Storage**

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Store below 25°C. Protect from light and moisture.

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**Medicine Classification**

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Prescription Medicine

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**Name and Address**

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Arrow Pharmaceuticals (NZ) Limited  
Mount Eden Central Business Park  
33a Normanby Road, Mt. Eden  
Auckland, New Zealand

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**Date of preparation**

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20 September 2010