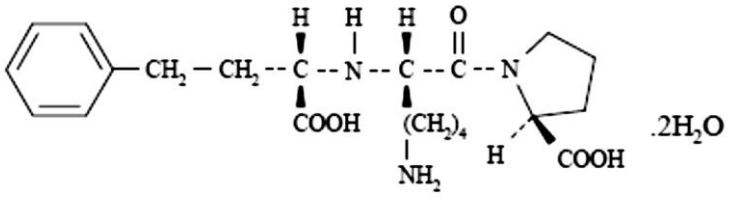
TERRY WHITE CHEMISTS LISINOPRIL TABLETS

NAME OF THE MEDICINE

Lisinopril dihydrate.

Chemical Name: *N*-[*N*-[(1*S*)-1-carboxy-3-phenylpropyl]-L-lysyl]-L-proline dehydrate.

Structural Formula:



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

Molecular Weight: 441.53

CAS Registry Number: 83915-83-7

DESCRIPTION

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

Each tablet contains lisinopril dihydrate as the active ingredient. In addition, each tablet contains the following inactive ingredients: calcium hydrogen phosphate, Mannitol, maize starch, magnesium stearate and iron oxide red (C177491).

PHARMACOLOGY

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).

Mechanism of Action

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 ll. Angiotensin ll also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of plasma angiotensin ll 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 ll 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, 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 differences 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 in diabetic patients is mediated by a reduction in blood pressure as well as a direct mechanism on the renal 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).

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 1 to 2 hours after oral administration of an individual dose of lisinopril, with peak reduction of blood pressure achieved by 6 hours. Although an antihypertensive effect was observed 24 hours after dosing with recommended single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, in all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing.

In some patients achievement of optimal blood pressure reduction may require 2 to 4 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 pre-treatment levels.

Two dose-response studies utilising a once daily regimen were conducted in 438 mild to moderate 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 10, 20 or 80 mg of lisinopril. 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 ¾ 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 blacks than in Caucasians.

In haemodynamic studies in patients with 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, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

Pharmacokinetics

Following oral administration, peak serum concentrations of lisinopril occur within about 7 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 inter-patient 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 is below 30 mL/min. Above this glomerular filtration rate, 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 (approximately doubled) higher 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 14C 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 foetuses.

CLINICAL TRIALS

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 equal to or less than 35%) or heart failure and to improve survival, based on the outcome of the GISSI-3 trial. The Gruppo Italiano per lo Studio della Sporavvienza nell'Infarto Miocardico (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 (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 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 6 weeks of either: 1) lisinopril alone (n = 4841), 2) nitrates alone (n = 4869), 3) lisinopril plus nitrates (n = 4841), or 4) open control (n = 4843). 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 ≤ 100 mmHg), severe heart failure, cardiogenic shock, and renal dysfunction (serum creatinine > 2 mg/dL and/or proteinuria > 500 mg/24 hr). Doses of lisinopril were adjusted as necessary according to protocol (see **DOSAGE AND ADMINISTRATION**).

Study treatment was withdrawn at 6 weeks except where clinical conditions indicated continuation of treatment.

The primary outcomes of the trial were the overall mortality at 6 weeks and a combined endpoint at 6 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 $\leq$ 35% or an akinetic-dyskinetic [A-D] score $\geq$ 45%. Patients receiving lisinopril (n = 9646), alone or with nitrates, had an 11% lower risk of death (2p [two-tailed] = 0.04) compared to patients receiving no lisinopril (n = 9672) (6.4% vs. 7.2%, respectively) at 6 weeks. The reduction in mortality at 6 months was not significant, but this was not a primary outcome measure. Although patients randomised to receive lisinopril for up to 6 weeks also fared numerically better on the combined end-point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up

echocardiography, and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomised to 6 weeks of lisinopril, preclude any conclusion about this endpoint.

Patients with acute myocardial infarction, treated with lisinopril, had a higher (9.0% vs. 3.7%) incidence of persistent hypotension (systolic blood pressure < 90 mmHg for more than 1 hr) and renal dysfunction (2.4% vs. 1.1%) in-hospital and at 6 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 20-59 years with insulin dependent diabetes mellitus (IDDM) and normoalbuminuria or microalbuminuria. The study recruited patients with a DBP in the range 75-90 mmHg inclusive provided that the SBP was ≤ 155 mmHg. Patients received either lisinopril 10 mg od or matching placebo for 2 years. Titration up to 20 mg od of lisinopril or 2 placebo tablets was permitted if sitting DBP had not reached the target value of less than 75 mmHg after 3 months of treatment. Nifedipine treatment (20 mg bd) was initiated if the BP remained inadequately controlled (SBP > 160 mmHg, DBP > 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 6 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 µg/min (p = 0.03) when adjusted for baseline AER and centre. After adjustment for DBP 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 (HbA_{1C} < 7%) or with a baseline DBP > 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 = 0.10. 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 non-protocol specified subgroup analysis in patients with baseline microalbuminuria (AER 20-200 µg/min) and endpoint AER the absolute difference in mean AER between the lisinopril group (n = 39) and the placebo group (n = 34) was 38.5 µg/min (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 and morbidity 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 3164 patients, with a median follow-up period of 46 months for surviving patients, statistically non-significant reductions were observed in the primary endpoint 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. NYHA classification (a measure of quality of life) did not differ between treatment groups.

INDICATIONS

Hypertension

Lisinopril is indicated in the treatment of mild to moderate essential hypertension. It may be used alone or concomitantly with other classes of antihypertensive agents. Sufficient data have not been provided to support the use of lisinopril in severe hypertension or renovascular hypertension.

Congestive Heart Failure

Lisinopril is also indicated in the treatment of heart failure. In such patients, it is recommended that lisinopril be administered together with a diuretic.

Acute Myocardial Infarction

Lisinopril is indicated for the treatment of acute myocardial infarction in haemodynamically stable patients, defined as patients who are not in cardiogenic shock and who have a systolic blood pressure greater than 100 mmHg. Lisinopril may be initiated within 24 hours of an acute myocardial infarction.

CONTRAINDICATIONS

Lisinopril is contraindicated in:

- Patients who are hypersensitive to lisinopril or any other ingredient listed under PRESENTATIONS AND STORAGE CONDITIONS.
- Patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor.
- Patients with hereditary or idiopathic angioedema.
- Pregnancy (see PRECAUTIONS, Use in Pregnancy).
- Patients undergoing haemodialysis with polyacrylonitrile-metalylsulphonate 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-metalylsulphonate 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.

- In combination with aliskiren-containing medicines in patients with diabetes mellitus (type I or II) or with moderate to severe renal impairment (GFR<60ml/min/1 .73m2).

PRECAUTIONS

Anaphylactoid Reactions during Hymenoptera Desensitisation

Patients receiving ACE inhibitors during desensitisation (e.g. to hymenoptera venom) have sustained 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 angiotensin converting enzyme (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, the product

should be discontinued promptly and appropriate monitoring instituted to ensure complete resolution of symptoms prior to dismissing the patient. Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

In instances when swelling has been confined to the face and lips, the angioedema has generally resolved either 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

Angiotensin converting enzyme 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 that are salt/volume depleted because of renovascular disease, diuretic therapy, vomiting or diarrhoea, and in patients undergoing dialysis (see **PRECAUTIONS, Impaired Renal Function, Interactions with Other Medicines** and **ADVERSE EFFECTS**). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive azotemia, 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 supervision. Such patients should be followed closely for the first 2 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 a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can 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. These are patients with systolic blood pressure of 100 mmHg or lower or cardiogenic shock. During the first 3 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 less than 90 mmHg for more than 1 hour) then lisinopril should be withdrawn.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with aliskiren-containing medicines.

Dual blockade of the renin-angiotensin-aldosterone system by combining lisinopril with aliskiren is not recommended since there is an increased risk of hypotension, hyperkalaemia and changes in renal function (see Interactions with other medicines).

Neutropenia / Agranulocytosis

Another angiotensin converting enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression (including leucopenia/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 haematologic monitoring be considered in patients with diseases known to affect bone marrow function (e.g. renal dysfunction, collagen vascular disease, etc) and/or who are taking concomitant therapy known to be associated with bone marrow depression.

Impaired Renal Function

Changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death.

In patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed. These increases are usually reversible upon discontinuation of ACE treatment. ACE inhibitors should be avoided in patients with known or suspected bilateral renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or with bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces glomerular filtration pressure. Under these circumstances, renal function is dependent on angiotensin II-induced vasoconstriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration decreases, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

Some patients with no apparent pre-existing renovascular disease have developed increases in blood urea nitrogen and serum creatinine which is usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics.

Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic 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 µgmol/L and/or proteinuria exceeding 500 mg/24 hr. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265 µgmol/L or a doubling from the pre-treatment value) then the physician should consider withdrawal of lisinopril.

Evaluation of the hypertensive patient should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**). In patients with renal artery stenosis, if a deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery stenosis present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

It is possible that in patients with compromised renal function who are being treated with NSAIDs, the co-administration of lisinopril may result in a further deterioration of renal function. This may result in an increase in serum potassium, but it appears that these effects are usually reversible.

Combination use of ACE Inhibitors or Angiotensin Receptor Antagonists, Anti-Inflammatory Drugs & 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.

Impaired Liver Function

Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with other ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

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

Hyperkalaemia

Because the ACE inhibitors decrease the formation of Angiotensin II and the subsequent production of aldosterone, serum potassium concentrations exceeding 5.5mEq/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. Diabetics, and elderly diabetics particularly, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may co-exist 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 / 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 (non-productive) irritating cough has been reported with ACE inhibitors. In various studies, the incidence of cough varies depending upon 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 maculo-papular pruritic rashes and sometimes photosensitivity 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 1 to 3 months despite continued treatment.

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.

Effects on Fertility

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

Use in Pregnancy (Category D)

As with all ACE inhibitors, lisinopril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with lisinopril and avoided during treatment.

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during 1st trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

Data, however, show that ACE inhibitors cross the human placenta. Post-marketing experience with all ACE inhibitors suggests that exposure *in utero* may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death *in utero*. Adverse effects appear to be most likely in the 2nd and 3rd trimesters.

When ACE inhibitors have been used during the 2nd and 3rd trimesters of pregnancy, there have been reports of foetal hypotension, renal failure, hyperkalaemia, skull hypoplasia and death. It is not known whether exposure limited to the first trimester can adversely affect foetal outcome.

Oligohydramnios has been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine 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 ^{14}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 nursing mother.

Paediatric Use

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

Carcinogenicity

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.

Genotoxicity

Lisinopril was not genotoxic in assays for gene mutations, chromosomal damage and DNA damage.

Effect on Ability to Drive and Use Machines

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

Information for 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, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

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 physician.

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

Hyperkalaemia

Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia

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

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.

INTERACTIONS WITH OTHER MEDICINES

Antihypertensive Agents

When combined with other antihypertensive agents, additive falls in blood pressure may occur.
The combination of lisinopril with aliskiren-containing medicines should be avoided (see Contraindications and Precautions).

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 in 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 co-administered 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.

Gold

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

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS)

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 (e.g. elderly patients or patients who are volume depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration in renal function, including possible renal failure. These effects are usually reversible.

These interactions should be considered in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with diuretics and ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.

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.

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 neurone 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 co-administration is indicated they should be used with caution and the patient's serum potassium should be monitored frequently.

Antidiabetics

Epidemiological studies have suggested that concomitant administration of ACE inhibitors 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 weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored for hypoglycaemia, especially during the first month of treatment with an ACE inhibitor.

ADVERSE EFFECTS

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 to

biochemical changes related to impaired renal function (hyperkalaemia and increased serum creatinine) as would be expected with ACE inhibitor therapy.

The adverse events which occurred in controlled clinical trials with lisinopril are taken from the case reports of 3702 patients (2633 patients with hypertension, 636 patients with congestive heart failure and 433 diabetes patients) and may be grouped as follows:

Hypertension (2633 patients)

More Common (3-10%)	**Less Common (1-3%)**	**Rare (<1%)**
Nervous System dizziness headache	Body as a Whole asthenia / fatigue Cardiovascular System chest pain Digestive System diarrhoea nausea vomiting Respiratory System cough Skin rash	Cardiovascular System hypotension orthostatic effects angina oedema palpitation rhythm disturbances Digestive System dyspepsia anorexia constipation flatulence Nervous System paraesthesia depression somnolence insomnia vertigo Respiratory System dyspnoea orthopnoea Skin pruritus Musculoskeletal System muscle cramps back pain leg pain shoulder pain Other blurred vision fever flushing gout decreased libido malaise

Congestive Heart Failure (636 patients)

The most common adverse reaction occurring in this patient population was dizziness (14.2%). The other adverse reactions were:

More Common (3-10%)	Less Common (1-3%)	Rare (<1%)
Nervous System headache Cardiovascular System hypotension chest pain angina Digestive System diarrhoea nausea Respiratory System cough dyspnoea Skin rash Body as a Whole asthenia / fatigue	Cardiovascular System orthostatic effects oedema palpitation Digestive System vomiting dyspepsia anorexia Nervous System paraesthesia depression insomnia Skin pruritus Musculoskeletal System muscle cramps back pain leg pain Other blurred vision fever gout malaise	Cardiovascular System rhythm disturbances Digestive System constipation flatulence Nervous System somnolence vertigo Respiratory System orthopnoea Musculoskeletal System shoulder pain Other flushing decreased libido

Renal and Retinal Complications of Diabetes Mellitus (433 patients)

Adverse events from 2 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 (>3-10%)	Less Common (1-3%)	Rare (<1%)
Body as a Whole abdominal pain flu syndrome	Body as a Whole accidental injury asthenia back pain chest pain fever headache infection pain	Body as a Whole generalised oedema neck pain pelvic pain
Nervous System dizziness		Cardiovascular System angina pectoris cerebral ischaemia hypertension palpitation
Respiratory System bronchitis increased cough pharyngitis	Cardiovascular System tachycardia	Digestive System constipation flatulence gastritis vomiting
	Digestive System diarrhoea dyspepsia gastroenteritis nausea	
	Metabolic & Nutritional Disorders hyperglycaemia hypoglycaemia	Skin & Appendages Eczema
	Musculoskeletal System arthritis myalgia	Metabolic & Nutritional Disorders hyperlipidaemia hypoglycaemic reaction peripheral oedema
	Nervous System vertigo	Musculoskeletal System arthrosis bursitis pathological fracture tendon disorder
	Respiratory System dyspnoea rhinitis sinusitis	Nervous System anxiety depression hypertonia paraesthesia
	Skin & Appendages rash	Special Senses ear disorder taste perversion
	Urogenital System cystitis ostitis media impotence urinary tract infection	Urogenital System dysuria haematuria kidney pain

Hypersensitivity / Angioneurotic Oedema

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

The following adverse reactions have been reported during post-marketing experience with a frequency of common (≥1% to <10%):

Renal and urinary disorders

Renal dysfunction

The following adverse reactions have been reported during post-marketing experience with a frequency of uncommon (≥0.1% to <1%):

Metabolism and nutrition disorders

Hyperkalaemia

Cardiac and vascular disorders

Syncope in the hypertensive population, while in the congestive heart failure population the frequency of syncope is common.

Nervous System and psychiatric disorders

Mood alterations (including depressive symptoms); taste disturbance, sleep disturbances, hallucinations.

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

Cardiovascular

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

Digestive System

Abdominal pain; dry mouth; hepatitis (hepatocellular and cholestatic) very rarely this may progress to hepatic failure; jaundice; pancreatitis

Endocrine disorders

Inappropriate antidiuretic hormone secretion

Musculoskeletal System

Joint pain.

Nervous System and psychiatric disorders

Mental confusion; stroke; olfactory disturbance.

Respiratory System

Bronchitis; bronchospasm; nasal congestion; pharyngeal pain; sinusitis; rhinitis.

Skin

Alopecia; urticaria; diaphoresis; cutaneous pseudolymphoma; psoriasis and severe skin disorders have been reported, including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

Urogenital System

Uraemia; oliguria/anuria; proteinuria; acute renal failure; impotence; urinary tract infection.

Body as a Whole

A symptom complex has been reported which may include fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, an elevated erythrocyte sedimentation rate, eosinophilia and leukocytosis. Rash, photosensitivity, or other dermatologic 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 12.0% of patients with congestive heart 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 co-existed, have occurred.

Other (Causal Relationship Unknown)

Rarely, elevations of liver 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.

DOSAGE AND ADMINISTRATION

Since there is no clinically significant effect of food on the absorption of lisinopril, the tablets may be administered before, during or after meals. Lisinopril should be administered in a single daily dose. As the 5 mg lisinopril tablets do not have a breakline, alternative lisinopril products should be used if a 2.5 mg dose is required. The 5 mg tablets **must not** be broken in half to give a 2.5 mg dose.

Essential Hypertension

In patients with uncomplicated essential hypertension not on diuretic therapy, the usual recommended starting dose is 5 to 10 mg. The usual maintenance dosage is 10 to 20 mg/day administered as a single daily dose. Dosage should be adjusted at 2 to 4 week intervals according to blood pressure response. In some patients doses up to 40 mg/day may be required. If blood pressure is not controlled with lisinopril, a low dose of a diuretic may be added. Hydrochlorothiazide (12.5 mg) has been shown to provide an additive effect. After addition of a diuretic, the dose of lisinopril may be reduced.

Diuretic-Treated or Severely Salt / Volume Depleted Patients

Symptomatic hypotension following the initial dose of lisinopril may occur occasionally in patients receiving concomitant diuretics. The diuretic should be discontinued if possible, for 2 to 3 days before beginning therapy with lisinopril (see **PRECAUTIONS**). In hypertensive patients in whom the diuretic cannot be discontinued, the initial dose of lisinopril should be 2.5 mg, followed then by 5 mg. The subsequent dosage of lisinopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed gradually.

Dosage Adjustment in Renal Impairment

The usual dose of lisinopril is recommended for patients with a creatinine clearance > 30 mL/min.

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in the following table:

Creatinine Clearance (mL/min)	Starting Dose (mg/day)
30 – 70	5.0 – 10
10 – 30	2.5 – 5
< 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 20 mg daily.

Dosage in the Elderly

In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of lisinopril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.

Congestive Heart Cardiac Failure

Note: Treatment of heart failure with lisinopril should be initiated under close medical supervision.

In patients not adequately controlled by diuretics (and digitalis, where indicated), lisinopril may be added with a starting dose of 2.5 mg once a day. Dose adjustment should be increased:

- by increments of no greater than 10 mg
- at intervals of no less than 2 weeks

The usual dosage is 5-20 mg/day administered as a single dose. The dose of lisinopril should not be titrated according to symptoms, as higher doses may not give additional symptomatic relief. The optimal upper dose has not been determined; 35 mg/day has been shown to be more effective than 5 mg/day but there is no evidence regarding the effectiveness of intermediate doses.

Patients at a high risk of symptomatic hypotension, e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia 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 (120 mmHg 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 **PRECAUTIONS**). If hypotension occurs (systolic blood pressure less than or equal to 100 mmHg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour) lisinopril should be withdrawn.

Dosing should continue for 6 weeks. Patients who develop symptoms of heart failure should continue with lisinopril (see **DOSAGE AND ADMINISTRATION**, **Congestive Heart Failure**).

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and a beta-blocker.

Lisinopril is compatible with intravenous or transdermal glyceryl trinitrate.

OVERDOSAGE

Symptoms

There are no data on overdosage in humans. The most likely manifestation of overdosage would be hypotension.

Treatment

The usual treatment for hypotension would be intravenous infusion of normal saline solution.
Lisinopril may be removed from the general circulation by haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Terry White Chemists Lisinopril tablets are intended for oral administration.
Each tablet contains 5mg, 10mg or 20mg Lisinopril dehydrate as active ingredient.

5 mg tablets
Light pink coloured, circular, biconvex, uncoated tablets with “5” embossed and break line on one side and “BL” embossing on other side.
Blister packs (PVC/Al) of 10, 14, 28,30, 50, 56, 84 and 100 tablets (AUST R 213396).

10 mg tablets
Light pink, circular, biconvex, uncoated tablets with “10” embossed on one side and “BL” embossing on other side.
Blister packs (PVC/Al) of 10, 14, 28,30, 50, 56, 84 and 100 tablets (AUST R 213397).

20 mg tablets
Pink, circular, biconvex, uncoated tablets with “20” embossed on one side and “BL” embossing on other side.
Blister packs (PVC/Al) of 10, 14, 28,30, 50, 56, 84 and 100 tablets (AUST R 213398).

Alternative lisinopril products should be used if a 2.5 mg dose is required. The 5 mg tablets **must not** be broken in half to give a 2.5 mg dose.

Not all strengths or pack sizes may be available.

Storage

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 21 August 2008

Date of most recent amendment: 17 February 2015