

AUSTRALIAN PI – FIBSOL (lisinopril dihydrate)

1 NAME OF THE MEDICINE

Lisinopril dihydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Fibsol tablets come in three strengths and contain lisinopril dihydrate equivalent to 5 mg, 10 mg or 20 mg of lisinopril.

For full list of excipients, see section 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

Fibsol 5 White, round tablet, marked L | 5 on one side and > on the other side.

Fibsol 10 White, round tablet, marked L | 10 on one side and > on the other side.

Fibsol 20 White, round tablet, marked L | 20 on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension.

Treatment of hypertension. Lisinopril 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.

Treatment of heart failure. In such patients, it is recommended that lisinopril be administered together with a diuretic.

Acute myocardial infarction.

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.

4.2 DOSE AND METHOD OF 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.

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 in a single daily dose. Dosage should be adjusted at two to four 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 or 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 two to three days before beginning therapy with lisinopril (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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.

Impaired renal function. The usual dose of lisinopril is recommended for patients with a creatinine clearance > 30 mL/minute. Dosage in-patients with renal impairment should be based on creatinine clearance as outlined below.

If creatinine clearance is between 70 and 30 mL/minute then the starting dose should be 5 to 10 mg/day.

If creatinine clearance is between 30 and 10 mL/minute then the starting dose should be 2.5 to 5 mg/day.

If creatinine clearance is less than 10 mL/minute (including patients on dialysis) then the starting dose should be 2.5 mg/day. (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.

Use 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 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 10mg and at intervals of no less than 2 weeks.

The usual dosage is 5 to 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; 35mg/day has been shown to be more effective than 5mg/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 three days after the infarct should be given a lower dose (2.5 mg) orally (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 < 90 mmHg for more than one hour), lisinopril should be withdrawn.

Dosing should continue for six weeks. Patients who develop symptoms of heart failure should continue with lisinopril (see Congestive cardiac failure, above). 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to lisinopril or any other component of lisinopril.
- History of hereditary and/or idiopathic angioedema, anaphylactic/ anaphylactoid reactions or angioedema associated with previous treatment with an ACE inhibitor.
- Patients with hereditary or idiopathic angioedema.
- Pregnancy (see 4.6 FERTILITY, PREGNANCY AND LACTATION, 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 (non-productive) 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.

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. ACE inhibitors may have a lesser effect on blood pressure in black hypertensive patients than in non-black hypertensive patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema whilst receiving an ACE inhibitor.

Some drugs, if given concomitantly with ACE inhibitors may increase the risk of angioedema (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.8 ADVERSE EFFECTS). 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren should be avoided (see 4.3 CONTRAINDICATIONS and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Aortic stenosis/Hypertrophic cardiomyopathy

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

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.

Use in hepatic impairment

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.

Use in renal impairment

Changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive cardiac 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 azotaemia 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 inhibitor 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 micromol/L and/or proteinuria exceeding 500 mg/24 hours. If renal dysfunction develops during treatment with lisinopril (serum creatinine concentration exceeding 265 micromol/L or a doubling from the pre-treatment value), the doctor should consider withdrawal of lisinopril. Evaluation of the hypertensive patient should always include assessment of renal function (see 4.2 DOSE AND METHOD OF ADMINISTRATION). In patients with renal artery stenosis, if a deterioration in renal function has occurred after treatment with one ACE inhibitor, 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.

Use in the elderly

No data available.

Paediatric use

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

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.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs that may increase the risk of angioedema: Concomitant treatment of ACE inhibitors with mammalian target of rapamycin (mTOR) inhibitors (e.g. temsirolimus, sirolimus, everolimus) or neutral endopeptidase (NEP) inhibitors (e.g. racecadotril) or tissue plasminogen activator may increase the risk of angioedema.

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.

The combination of lisinopril with other antihypertensive medicines may increase the antihypertensive effect, especially in combination with diuretics.

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.

Nonsteroidal anti-inflammatory drugs: Drugs with prostaglandin synthetase inhibitory properties (e.g. indomethacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors. 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 NSAIDs including selective COX-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors, including lisinopril, 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.

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 (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hyperkalaemia): 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, or other drugs that may increase serum potassium levels (e.g. heparin, cotrimoxazole) can

increase the risk of hyperkalaemia. Therefore, if co-administration is indicated these agents should be used with caution and the patient's serum potassium should be monitored frequently.

Antihypertensive agents: When combined with other antihypertensive agents, additive falls in blood pressure may occur. Clinical trial data has shown that the dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

The combination of lisinopril with aliskiren-containing medicines should be avoided (see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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. 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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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)

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

If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced with 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. However, data 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 second and third trimesters.

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 with no exposure.

When ACE inhibitors have been used during the second and third 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 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 ¹⁴C 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 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. Hypersensitivity/ angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported uncommonly (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In very rare cases, intestinal angioedema has been reported with ACE inhibitors, including lisinopril.

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

Genitourinary: Renal dysfunction.

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

Metabolic: Hyperkalaemia

Cardiovascular: Syncope in the hypertensive population, while in the congestive heart failure population the frequency is common. Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE); tachycardia.

Gastrointestinal: Taste disturbance

Nervous system: Mood alterations (including depressive symptoms), sleep disturbances, hallucinations.

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

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

Patients receiving lisinopril who develop jaundice or marked elevation of hepatic enzymes should discontinue lisinopril and receive appropriate medical follow up.

Endocrine: Syndrome of inappropriate antidiuretic hormone secretion.

Metabolic: Cases of hypoglycaemia in diabetic patients on oral antidiabetic agents or insulin have been reported (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Musculoskeletal. Joint pain.

Nervous system. Mental confusion, stroke, olfactory 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, erythema multiforme and cutaneous pseudolymphoma.

Genitourinary. 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 antinuclear antibody (ANA) test, an elevated erythrocyte sedimentation rate (ESR), eosinophilia and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Laboratory test findings: Hyperkalaemia, haemolytic anaemia.

Immune system: anaphylactic/ anaphylactoid reaction.

Clinical laboratory test findings.

Serum electrolytes: Hyperkalaemia (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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).

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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 pre-treatment 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.

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 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 Sopravvivenza 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 4.2 DOSE AND METHOD OF 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 non-protocol 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

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.

Distribution

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.

Metabolism

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine.

Excretion

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 4.2 DOSE AND METHOD OF ADMINISTRATION) Lisinopril can be removed by haemodialysis.

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

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Fibsol tablets contain the following excipients: mannitol, calcium hydrogen phosphate dihydrate, maize starch, pregelatinised maize starch, colloidal anhydrous silica and magnesium stearate. The tablets are gluten free.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

Fibsol 5, PVC/PVDC/Al blister packs of 30.

Fibsol 10, PVC/PVDC/Al blister packs of 30.

Fibsol 20, PVC/PVDC/Al blister packs of 30.

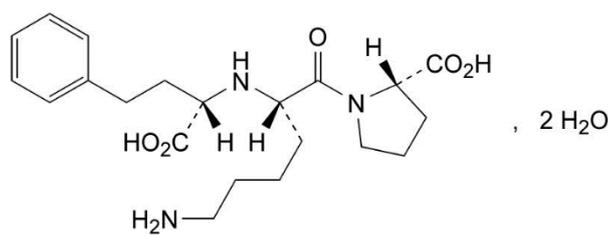
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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:



$C_{21}H_{31}N_3O_5 \cdot 2H_2O$

Molecular weight: 441.53

CAS number

CAS No.: 83915-83-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Arrow Pharma Pty Ltd

15 – 17 Chapel Street

Cremorne VIC 3121

9 DATE OF FIRST APPROVAL

23 August 2004.

10 DATE OF REVISION

29th March 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3, 4.4, 4.5 & 4.8	Safety related updates