AUSTRALIAN PI – FOSIPRIL (fosinopril sodium)

1 NAME OF THE MEDICINE

Fosinopril sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fosipril tablets come in two strengths, containing either 10 mg or 20 mg of fosinopril sodium.

The tablets contain lactose monohydrate. For full list of excipients, see section 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

Fosipril 10 White oval tablet, embossed with FI, partial score, 10 on one side and a partial score on the other side.

Fosipril 20 White capsule-shaped tablet, embossed with FI 20 on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension.

Treatment of mild to moderate hypertension.

Fosinopril is effective alone as initial therapy or in combination with other antihypertensive agents. The antihypertensive effects of fosinopril and diuretics used concomitantly are approximately additive.

Data have not been provided to support the use of fosinopril in severe or renovascular hypertension.

Heart failure.

Management of heart failure when added to conventional therapy, including diuretics.

4.2 DOSE AND METHOD OF ADMINISTRATION

Hypertension.

Patients not being treated with diuretics. The recommended initial dose of fosinopril is 10 mg once a day. The usual dose range required to maintain blood pressure control is 10 to 40 mg/day administered as a single dose. Fosinopril should be taken at the same time each day. Dosage should then be adjusted according to blood pressure response. If blood pressure is not adequately controlled with fosinopril alone, a diuretic may be added.

Patients currently being treated with diuretics (or who may be volume depleted). The diuretic should preferably be discontinued for several days prior to beginning therapy with fosinopril in order to reduce the risk of an excessive hypotensive response. (See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) If blood pressure is inadequately controlled after an observation period of approximately four weeks, diuretic therapy may be resumed. Alternatively, if diuretic therapy cannot be discontinued, an initial dose of fosinopril 10 mg should be used with careful medical supervision for several hours and until blood pressure has stabilised. (See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Since concomitant administration of fosinopril with potassium supplements, potassium containing salt substitutes or potassium sparing diuretics may lead to increases in serum potassium, they should be used with caution.

Heart failure.

The recommended initial dose of fosinopril is 10 mg once daily. Therapy should be initiated under close medical supervision. If the initial dose of fosinopril is well tolerated, the dose may be titrated at weekly intervals according to clinical response up to 40 mg once daily. The appearance of hypotension after the initial dose should not preclude careful dose titration with fosinopril following effective management of hypotension. Fosinopril should be used in conjunction with a diuretic (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hypotension).

Impaired renal function.

In patients with impaired renal function, the total body clearance of fosinopril diacid is approximately 50% slower than in patients with normal renal function. However, within the population of renally impaired patients, the body clearance of fosinopril diacid does not differ appreciably with the degree of renal insufficiency, including endstage renal failure (creatinine clearance < 10 mL/minute/1.73 m2), since diminished renal elimination is partially compensated by increased hepatobiliary elimination. The relatively greater clearance by the hepatobiliary route of active fosinopril diacid when compared with total clearance in patients with renal failure permits use of an initial dose of 5 to 10 mg. An initial dose of 5 mg is preferred in heart failure patients with moderate to severe renal failure or those who have been vigorously diuresed. In patients with congestive heart failure and chronic renal failure, subsequent dosage adjustments should be made to control the patient's heart failure under careful clinical monitoring including frequent determination of renal function.

Impaired hepatic function.

It is advisable to initiate treatment at a dose of 10 mg in patients with mild to moderate impairment. Although the rate of hydrolysis of fosinopril diacid may be slowed, the extent of hydrolysis is not appreciably reduced in patients with hepatic impairment. In this group of patients, there is evidence of reduced hepatic clearance of fosinopril diacid with compensatory increase in renal excretion.

4.3 CONTRAINDICATIONS

Hypersensitivity to fosinopril sodium, to any other ACE inhibitor (e.g. a patient who has experienced angioedema during therapy with any other ACE inhibitor) or to any of the tablet excipients; history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor; pregnancy (see 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Pregnancy).

The concomitant use of ACE inhibitors with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anaphylactoid and Possibly Related Reactions

Head and Neck Angioedema.

Severe life-threatening angioedema has been reported rarely with ACE inhibitors. The overall incidence is approximately 0.1 to 0.2%. 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. In the majority of reported cases, the symptoms occurred during the first week of therapy. However, the onset of angioedema may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom free intervals. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Angioedema may occur with or without urticaria but usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including fosinopril. In such cases the product should be discontinued promptly and appropriate monitoring instituted to ensure complete resolution of symptoms. 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. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and can be fatal. Emergency therapy, including but not necessarily limited to adrenaline and oxygen administration, should be carried out promptly or the patient hospitalised. Patients who respond to medical treatment should be observed carefully for a possible re-emergence of symptoms of angioedema.

There are reports where changing the patient over to another ACE inhibitor was followed by recurrence of oedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class. (See 4.3 CONTRAINDICATIONS)

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

Patients receiving co-administration of ACE inhibitor and mTOR (mammalian target rapamycin) inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk for angioedema.

Intestinal angioedema.

Intestinal angioedema has been reported rarely in patients treated with ACE-inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases, there was no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including CT scans or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during desensitisation.

Two patients undergoing desensitising treatment with Hymenoptera venom while receiving another ACE inhibitor, enalapril, sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high flux dialysis/ lipoprotein aphaeresis membrane exposure.

Patients haemodialysed using high flux polyacrylonitrile (AN69) membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors.

Anaphylactoid reactions have also been reported in patients undergoing low density lipoprotein aphaeresis with dextran sulfate absorption. These combinations should therefore be avoided, either by use of a different class of medication or alternative membranes (e.g. cuprophane or polysulfone (PSF)) for haemodialysis.

Neutropenia/agranulocytosis.

Agranulocytosis and bone marrow depression (including leucopenia/ neutropenia) have been reported with ACE inhibitors. These have mostly occurred in patients with pre-existing impaired renal function, collagen vascular disease, immunodepressant therapy or a combination of these complicating factors. Most episodes of leucopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease, renal disease (serum creatinine greater than or equal to 180 micromol/L) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Hypotension.

Fosinopril can cause symptomatic hypotension. Like other ACE inhibitors, fosinopril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result

of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with fosinopril. A transient hypotensive response is not a contraindication to further doses which may be given without difficulty after replacement of salt and/or volume.

The risk of an exaggerated hypotensive response (and also hyponatraemia) can be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to initiation of treatment with fosinopril. If diuretics are continued, the patient should be closely observed for several hours following an initial dose and until blood pressure has stabilised.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotaemia and, rarely, with acute renal failure and death. In such patients, fosinopril therapy should be started under close medical supervision; they should be followed closely for the first two weeks of treatment and whenever the dose of fosinopril or diuretic is increased.

Consideration should be given to reducing the diuretic dose in patients with normal or low blood pressure who have been treated vigorously with diuretics or who are hyponatraemic. Hypotension is not per se a reason to discontinue fosinopril. Some decrease of systemic blood pressure is not an uncommon observation upon initiation of fosinopril treatment in heart failure. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilises within a week or two, and generally returns to pre-treatment levels without a decrease in therapeutic efficacy.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Fosinopril treatment usually can be continued following restoration of blood pressure and volume.

Hyperkalaemia.

Because the ACE inhibitors decrease the formation of angiotensin II, which results in decreased production of aldosterone, increase in serum potassium levels (> 5.5 mEq/L) are not unexpected with this class of drugs. Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium sparing diuretics or potassium supplements and/or consuming potassium containing salt substitutes; or those patients taking other medicines associated with an increase serum potassium (e.g. trimethoprim containing medicines). Diabetic patients, and particularly elderly diabetic patients, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may coexist with hyperkalaemia. It is recommended that patients undergoing ACE inhibitor treatment should have measurement of serum electrolytes (including potassium, sodium and urea) from time to time. This is more important in patients taking diuretics.

Cough.

A persistent dry (non-productive) irritating cough has been reported with all ACE inhibitors in use. The frequency of reports has been increasing since cough was first recognised as a side effect of ACE inhibition. In various studies, the incidence of cough varies between 2 and > 9% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night. The cough is more common in women (who account for two-thirds of the reported cases). Patients who cough may have increased bronchial

reactivity compared to those who do not cough. The observed higher frequency of this complication in non-smokers may be due to a higher level of tolerance to cough by smokers.

The mechanism of this adverse reaction is not clear but most likely to be secondary to the effects of converting enzyme inhibitor on kinins (bradykinin and/or prostaglandin) resulting in stimulation of the pulmonary cough reflex. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor. The reaction may recur on rechallenge with another ACE inhibitor but this is not invariably the case. A change in antihypertensive regimen may be required in severe cases.

Surgery/anaesthesia.

In patients undergoing major surgery or anaesthesia who are being treated with agents that produce hypotension, ACE inhibitors may block angiotensin II formation secondary to compensatory renin release and thus may augment the hypotensive response. If hypotension occurs, and is considered to be due to this mechanism, it can be corrected by volume expansion.

Dermatological reactions.

Dermatological reactions characterised by maculopapular pruritic rashes and sometimes photosensitivity have been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome) have been reported. A causal relationship is difficult to assess.

Patients who developed a cutaneous adverse event with one ACE inhibitor may be free of reaction when switched to another drug of the same class, but there are also reports of cross reactivity.

Taste disturbances (dysgeusia).

Taste disturbances were reported to be high (up to 12.5%) with high doses of another ACE inhibitor. The actual incidence of taste disturbance is probably low (< 0.5%) but data in this respect are scarce and difficult to interpret.

Taste disturbances with ACE inhibitors are described as suppression of taste or a metallic sensation in the mouth. The dysgeusia occurs usually in the first weeks of treatment and usually disappears within one to three months of treatment.

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 RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). If dual blockade therapy is considered absolutely 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 diabetes nephropathy.

Use in hepatic impairment

Patients with impaired liver function could develop elevated plasma levels of fosinopril. In a study in patients with alcoholic or biliary cirrhosis, the apparent total body clearance of fosinopril was decreased and the plasma AUC approximately doubled.

Rarely, ACE inhibitors have been associated with the syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical attention.

Use in renal impairment

As a consequence of inhibiting the renin angiotensin aldosterone system, 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 azotaemia but rarely with acute renal failure and/or death. In patients with congestive heart failure and pre-existing renal failure fosinopril, like other ACE inhibitors, should be used with caution. Although available data suggest minimal accumulation during ten days of therapy with fosinopril 10 mg daily, dosage reduction in this patient group may be necessary and renal function should be closely monitored.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of ACE treatment and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

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

ACE inhibitors have a real potential to delay progression of nephropathy in diabetic as well as in hypertensive patients. The antiproteinuric effect of ACE inhibitors could depend upon the dose, selective availability at the renal tissue site and on the patient's sodium status. Nevertheless, some ACE inhibitors have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium sparing diuretics or high doses of other diuretics, limited cardiac reserve, or treatment with an NSAID.

Evaluation of the hypertensive patient should always include assessment of renal function. (See 4.2 DOSE AND METHOD OF ADMINISTRATION) 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 another class of antihypertensive agent should be preferred.

Use in the elderly (over 65 years)

No dosage reduction is necessary in patients with clinically normal renal and hepatic function as no significant differences in the pharmacokinetic parameters or antihypertensive effect of fosinopril diacid have been found compared with younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Paediatric use

Safety and effectiveness in individuals less than 18 years old have not been established.

Effects on laboratory tests

Fosinopril may cause a false low measurement of serum digoxin levels with assays utilising the charcoal absorption method. Other kits which utilise the antibody coated tube method may be used instead. Therapy with fosinopril should be interrupted for a few days before carrying out tests of parathyroid function.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diuretics. Since the antihypertensive effects of ACE inhibitors are enhanced by diuretics, patients on diuretics, especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restrictions, on dialysis or with intravascular volume depletion, may occasionally experience excessive blood pressure reduction or hypotensive symptoms (e.g. dizziness) with the initiation of ACE inhibitor therapy. (See 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Hypotension)

Since increases in serum potassium have been observed with ACE inhibitors, including fosinopril, the potassium wasting effect of most diuretics may be blunted by concomitant ACE inhibitor therapy. Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride) should be used with caution when administered concomitantly with ACE inhibitors. Monitor serum potassium in such patients frequently.

Decreases in serum sodium and increases in serum creatinine occurred more frequently in patients receiving concomitant diuretics than in those treated with fosinopril alone.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics. The use of a renin-angiotensin 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 and periodically thereafter. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Lithium. Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. 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.

Hyperkalaemia

Potassium sparing diuretics, Potassium supplements, Potassium salts or other medicinal products or substitutes that may increase serum potassium levels (e.g. trimethoprim containing medicines) can increase the risk of hyperkalaemia. These supplements and salt substitutes should be used with caution, and serum potassium should be monitored frequently.

Antidiabetics. ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in diabetics. Glycemia levels should be monitored at the beginning of initiation therapy to adjust the dose of antidiabetic medications.

Dual Blockade of the Renin-Angiotensin-Aldosterone-System (RAAS). Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (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 (see 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Inhibitors of endogenous prostaglandin synthesis. It has been reported that indomethacin may reduce the antihypertensive effect of other ACE inhibitors, especially in cases of low renin hypertension. Other NSAIDs (e.g. aspirin) and selective COX-2 inhibitors may have a similar effect. In patients who are elderly, volume depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with the ACE-inhibitors, including fosinopril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving fosinopril and NSAID therapy.

Antacids. In a clinical pharmacology study, co-administration of an antacid (aluminium hydroxide, magnesium hydroxide and simethicone) with fosinopril reduced serum levels and urinary excretion of fosinopril diacid as compared with fosinopril administered alone, suggesting that antacids may impair absorption of fosinopril. Therefore, if concomitant administration of these agents is indicated, dosing should be separated by two hours.

Mammalian Target of Rapamycin (mTOR) Inhibitors. Patients taking concomitant mTOR inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk of angioedema.

Other agents. In pharmacokinetic interaction studies with nifedipine, propranolol, cimetidine, metoclopramide and propantheline, the bioavailability of fosinopril diacid was not altered by co-administration of fosinopril with any one of these drugs. In studies with concomitant administration of aspirin and fosinopril, the area under the curve (AUC) for unbound fosinopril diacid was not altered, however, the AUC for total (bound and unbound) fosinopril diacid and 48 hour cumulatory urinary excretion were reduced by 42%.

In pharmacokinetic studies in healthy volunteers, no clinically significant interactions occurred when fosinopril was co-administered with either digoxin or warfarin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There were no adverse reproductive effects in male and female rats treated with 15 to 60 mg/kg daily. There was no effect on pairing time prior to mating in rats until a daily dose of 240 mg/kg, a toxic dose, was given; at this dose, a slight increase in pairing time was observed.

Use in pregnancy (Category D)

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

When used in pregnancy, ACE inhibitors can cause injury and even death to the developing foetus.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure and death.

Oligohydramnios has also been reported, presumably resulting from decreased foetal function; oligohydramnios has been associated with foetal limb contractures, craniofacial malformations, hypoplastic lung development and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported.

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.

Use in lactation.

Ingestion of 20 mg daily for three days resulted in detectable levels of fosinopril diacid in human breast milk. Fosinopril should not be administered to breastfeeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects such as hypotension, dizziness and fatigue may interfere with the ability to drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Hypertension. Fosinopril has been evaluated for safety in more than 1,500 individuals, including 300 patients treated for one year or more. In placebo controlled clinical trials, the usual duration of therapy was two to three months.

In placebo controlled clinical trials (633 fosinopril treated patients) 3.3% of patients were discontinued from fosinopril and 1.2% from placebo due to any adverse experience.

Heart failure. In placebo controlled clinical trials of three to six months duration, the discontinuation rates due to any clinical or laboratory adverse event, except for heart failure, were 8.0 and 7.5% in fosinopril treated and placebo treated patients, respectively.

Clinical adverse experiences. During clinical trials with any fosinopril regimen, the incidence of adverse experiences in elderly patients (greater than or equal to 65 years old) was similar to that seen in younger patients.

Clinical adverse events (and consequent study discontinuations) occurring in patients treated with fosinopril alone in placebo controlled trials are summarised in Table 1. The incidences in columns A and B represent all clinical adverse events observed in hypertension trials, regardless of their attribution to study therapy, that occurred in at least 1% of patients. Columns C and D give the incidences for clinical adverse events to therapy occurring in at least 1% of patients treated with fosinopril in placebo controlled trials in heart failure.

Table 1: Percentage of patients with clinical adverse experiences in placebo controlled trials.

Adverse event	Incidence (%)* regardless of attribution in hypertension trials (discontinuation)		Incidence (%)[a] in heart failure trials (discontinuation)	
	Fosinopril (n=633)(A)	Placebo (n=172)(B)	Fosinopril (n=361)(C)	Placebo (n=373)(D)
General				
Fatigue	4.1 (0.6)	2.9	-	-
Chest pain[b]	1.9 (0.3)	1.2	2.2 (0.0)	1.6 (0.0)
Oedema	1.6 (0.0)	2.4	-	-
Viral infection	1.3 (0.2)	0.6	-	-
Pain	1.1 (0.0)	0.6	-	-
Weakness	-	-	1.4 (0.3)	0.5 (0.0)
Cardiovascular				
Rhythm disturbances, palpitations	1.8 (0.2)	1.2	1.4 (0.3)	0.8 (0.0)
Hypotension	-	-	4.4 (0.8)	0.8 (0.0)
Orthostatic hypotension	-	-	1.9 (0.0)	0.8 (0.0)
Angina pectoris	-	-	1.1 (0.3)	1.1 (0.0)
Dermatological				
Rash	2.2 (0.0)	0.0	1.4 (0.3)	2.1 (0.3)
Gastrointestinal				
Nausea/vomiting	4.3 (0.5)	2.9	2.2 (0.6)	1.6 (0.3)
Diarrhoea	4.1 (0.5)	2.9	2.2 (0.0)	1.3 (0.0)
Abdominal pain	2.0 (0.3)	2.4	-	-
Pyrosis	1.9 (0.0)	0.6	-	-
Musculoskeletal, connective tissue				

Adverse event	Incidence (%)* regardless of attribution in hypertension trials (discontinuation)		Incidence (%)[a] in heart failure trials (discontinuation)	
	Fosinopril (n=633)(A)	Placebo (n=172)(B)	Fosinopril (n=361)(C)	Placebo (n=373)(D)
Musculoskeletal pain	6.0 (0.2)	3.5	-	-
Myalgia	2.8 (0.2)	1.8	-	-
Nervous system				
Headache	8.4 (0.9)	11.0	-	-
Dizziness	3.8 (0.0)	1.2	11.9 (0.6)	5.4 (0.3)
Mood change**	2.7 (0.7)	1.8 (1.2)	-	-
Paraesthesia	1.6 (0.0)	0.0	-	-
Sleep disturbance	1.4 (0.2)	0.6	-	-
Respiratory				
Cough	7.1 (0.2)	3.5	9.7 (0.8)	5.1 (0.0)
Sinus abnormality	4.6 (0.0)	2.9	-	-
Upper respiratory infection	4.1 (0.0)	4.7	-	-
Rhinitis	3.8 (0.0)	2.9	-	-
Pharyngitis	3.9 (0.2)	1.7	-	-
Special senses				
Eye disturbances	1.6 (0.0)	1.2	-	-
Taste alterations	1.6 (0.0)	0.0	-	-
Visual disturbances	1.0 (0.0)	1.2	-	-
Genitourinary				
Abnormal urination***	1.3 (0.0)	1.2	-	-
Sexual dysfunction	1.7 (0.4)	1.2 (0.6)	-	-

* No significant differences between fosinopril and placebo group

** Includes stress reaction and nervousness

*** Includes changes in urinary frequency, polyuria and oligouria

[a] Clinical adverse events probably or possibly related or of uncertain relationship to therapy

[b] In heart failure trials, defined as non-cardiac

Other clinical adverse experiences reported with fosinopril and other ACE inhibitors follow, listed by body system.

General. Weakness, fever[+], hyperhidrosis, ecchymosis.

Cardiovascular. Sudden death*, cardiac/cardiorespiratory* arrest, shock (0.2%)*, angina/ myocardial infarction, cerebrovascular accident, hypertensive crisis, tachycardia, cardiac rhythm disturbances*, flushing, peripheral vascular disease, peripheral oedema*, hypertension*, syncope*, conduction disorder*.

[+] Seen both in hypertension and heart failure patients. In heart failure patients in the incidence described under *

* Clinical events probably or possibly related, or of uncertain relationship to therapy, occurring in 0.4 to 1% of patients (except as noted) treated with fosinopril in controlled clinical trials in heart failure (n=516) and less frequent, clinically significant events.

Hypotension, orthostatic hypotension, and syncope occurred in 0.1, 1.5 and 0.2%, respectively, of patients treated with fosinopril for hypertension. Hypotension or syncope was a cause for discontinuation of therapy in 0.3% of patients.

Dermatological. Pruritus[+], dermatitis, urticaria, photosensitivity.

Endocrine/ metabolic. Gout[+], sexual dysfunction*.

Foetal/Neonatal morbidity and mortality. The use of ACE inhibitors during pregnancy has been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported. More recently, prematurity, patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have been reported following exposure limited to the first trimester of pregnancy (see 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy).

Gastrointestinal. Bleeding, pancreatitis, hepatitis, tongue swelling, dysphagia, oral lesions, abdominal distension, appetite[+]/ weight change[+], constipation[+], flatulence[+], dry mouth[+].

Haematological. Lymphadenopathy.

Immunological. Angioedema (0.2%)[+].

Musculoskeletal. Arthritis, myalgia[+], weakness of an extremity[+].

Nervous/ psychiatric. Equilibrium disturbance, memory disturbance, drowsiness, confusion, depression*, paraesthesia*, vertigo*, behaviour change*, tremor*, cerebral infarction*, transient ischaemic attack*.

Respiratory. Dyspnoea, bronchospasm, pneumonia, pulmonary congestion, laryngitis/ hoarseness, epistaxis, rhinitis*, sinusitis*, tracheobronchitis*, pleuritis*, chest pain*.

A symptom complex of cough, bronchospasm, eosinophilia has been observed in two patients treated with fosinopril.

Special senses. Tinnitus, ear pain, vision disturbance*, taste disturbance*.

Genitourinary. Renal insufficiency, prostate disorder, abnormal urination*.

Laboratory tests Abnormalities. Leucopenia, neutropenia, eosinophilia, increased serum levels of liver function tests (transaminases, LDH, alkaline phosphatase and bilirubin), serum electrolytes: Hyperkalaemia, hyponatraemia (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Diuretics).

Renal function tests. Elevations, usually transient and minor, of blood urea nitrogen (BUN) and creatinine have been observed. In placebo controlled clinical trials, there were no significant differences in the number of patients experiencing increases in serum creatinine (outside the normal range or 1.33 times the pre-treatment value) between the fosinopril and placebo treatment groups.

In placebo controlled trials in hypertension, a urinary albumin greater than or equal to 2+ or greater than or equal to 2 times the pre-treatment value was seen in 2.8% of fosinopril treated and none of the placebo treated group. Increases in urinary albumin usually developed in patients with pre-existing proteinuria or diabetes and caused no clinical adverse effect.

Haematology. In controlled trials, a mean haemoglobin decrease of 0.13 g/dL was observed in fosinopril treated patients. In individual patients, decreases in haemoglobin or haematocrit were usually transient, small and not associated with symptoms. No patient was discontinued from therapy due to the development of anaemia.

Other. Leucopenia and eosinophilia have been reported; neutropenia (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Liver function tests. Elevations of transaminases, alkaline phosphatase and serum bilirubin have been reported. Fosinopril therapy was discontinued because of serum transaminase elevations in 0.7% of patients in hypertension studies. In the majority of cases, the abnormalities were either present at baseline or were associated with other aetiological factors. In those cases which were possibly related to fosinopril therapy, the elevations were generally mild and transient and resolved after discontinuation of therapy.

Post-Marketing Experience

During post-marketing surveillance, the following adverse reactions were detected:

Skin and sub-cutaneous tissue disorders: pemphigus, bullous pemphigoid.

Reporting Suspected Adverse Effects

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

No specific information is available on the treatment of overdosage with fosinopril; treatment should be symptomatic and supportive. Therapy with fosinopril should be discontinued and the patient closely monitored. Suggested measures include correction of hypotension by established procedures. Fosinopril is poorly removed from the body by haemodialysis or peritoneal dialysis.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Following absorption in humans and animals, fosinopril sodium is hydrolysed to the pharmacologically active fosinopril diacid, a specific competitive inhibitor of angiotensin converting enzyme.

ACE, a peptidyl dipeptidase, catalyses the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II. Angiotensin II is a potent vasoconstrictor and it also stimulates aldosterone secretion by the adrenal cortex, thereby contributing to sodium and fluid retention. The effects of fosinopril in hypertension appear to result primarily from inhibition of angiotensin II formation and decreased aldosterone secretion. Inhibition of ACE activity leads to decreased levels of angiotensin II, thereby resulting in diminished vasoconstriction, aldosterone secretion, peripheral vascular resistance, and sodium and fluid retention. Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal secretion results in increases in plasma renin activity. Decreased levels of aldosterone result in small increases of serum potassium.

While the mechanism through which fosinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, fosinopril has an antihypertensive effect even in patients with low renin hypertension. Although fosinopril was antihypertensive in persons of all races studied, black people who were hypertensive (usually a low renin hypertensive population) had a smaller average response to ACE inhibitor monotherapy than patients who were not black.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of fosinopril remains to be elucidated.

Administration of fosinopril to patients with mild to moderate hypertension has reduced both supine and standing blood pressures, usually without orthostatic effects. Symptomatic postural hypotension was infrequent, although it should be considered in salt and/or volume depleted patients. (See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Following oral administration of a single dose of fosinopril, the onset of an antihypertensive effect was seen within one hour and peak blood pressure reduction within two to six hours.

At the usual daily dose (10 to 40 mg/day), antihypertensive effects of fosinopril have been maintained for 24 hours. In some patients at lower doses, these effects may diminish toward the end of the dosing interval. (See 4.2 DOSE AND METHOD OF ADMINISTRATION).

For optimal blood pressure reduction, dosage may need to be adjusted during the early stages of treatment. (See 4.2 DOSE AND METHOD OF ADMINISTRATION).

The antihypertensive effect of fosinopril has been shown to continue during long-term therapy for at least two years.

As with other ACE inhibitors, abrupt withdrawal of fosinopril has not been associated with rapid increases in blood pressure.

The antihypertensive effects of fosinopril and diuretics used concurrently are approximately additive.

Serum ACE activity was inhibited by greater than or equal to 90% at two to twelve hours after single doses of fosinopril 10 to 40 mg. At 24 hours, serum ACE activity remained suppressed by 85, 93 and 93% in the 10, 20 and 40 mg dose groups, respectively.

In haemodynamic studies in hypertensive patients, after three months of therapy, responses (changes in blood pressure, heart rate, cardiac index and peripheral vascular resistance) to various stimuli (e.g. isometric exercise, 45 deg. head up tilt, and mental challenge) were unchanged compared to baseline, suggesting that fosinopril does not affect the activity of the sympathetic nervous system. Reduction in systemic blood pressure appears to have been mediated by a decrease in peripheral vascular resistance without reflex cardiac effects. Similarly, renal, splanchnic, cerebral and skeletal muscle blood flow were unchanged compared to baseline, as was glomerular filtration rate.

In patients with heart failure, the beneficial effects of fosinopril are thought to result primarily from suppression of the renin-angiotensin-aldosterone system; inhibition of the ACE produces decreases in both preload and afterload.

In heart failure patients fosinopril improves symptoms and exercise tolerance, reduces severity of heart failure, and decreases the frequency of hospitalisation for heart failure. The beneficial effect of fosinopril does not require the concomitant use of digoxin.

In a double blind, controlled trial among patients with heart failure treated with diuretics and with or without digoxin, the initial dose of fosinopril resulted in an acute decrease in pulmonary capillary wedge pressure (preload), and mean arterial blood pressure and systemic vascular resistance (afterload). Single daily doses of fosinopril maintained the positive haemodynamic effects throughout the 24 hour dosing interval among patients completing ten weeks of treatment. In addition, heart rate decreased from baseline and stroke volume index increased despite the reduced left ventricular filling pressure. No tachyphylaxis was seen.

Fosinopril improved exercise tolerance at 24 hours in two placebo controlled studies (271 patients with heart failure treated with fosinopril once daily) of up to six months duration, including one trial in which patients were not treated concomitantly with digoxin. Clinical manifestations of heart failure also improved, as measured by study withdrawals (risk reduction 66%, $p < 0.001$) or hospitalisations for worsening heart failure (risk reduction 66%, $p = 0.001$). Fosinopril reduced the need for additional diuretic to control symptoms of heart failure. Severity of heart failure, as measured by favourable changes in New York Heart Association classification, and symptoms of heart failure, including dyspnoea and fatigue, improved.

The effects of fosinopril on long-term mortality in heart failure have not been evaluated.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, fosinopril (the prodrug) is absorbed slowly. The absolute absorption of fosinopril averaged 36% of an oral dose. The primary site of absorption is the proximal small intestine (duodenum/ jejunum). The extent of absorption of fosinopril is essentially unaffected (but the rate may be slowed) by the presence of food in the gastrointestinal tract.

Distribution

In healthy subjects and renally impaired patients, hydrolysis of fosinopril to the active fosinopril diacid is rapid and complete. This biotransformation probably occurs in the gastrointestinal mucosa and liver. Although the rate of hydrolysis may be slowed, the extent of hydrolysis is not appreciably reduced in patients with hepatic impairment.

Metabolism

After an oral dose of radiolabelled fosinopril to healthy subjects, 75% of radioactivity in plasma was present as active fosinopril diacid, 20 to 30% as a glucuronide conjugate of fosinopril diacid, and 1 to 5% as a para-hydroxy metabolite of fosinopril diacid. In urine, 75% of the drug excreted was fosinopril diacid, and the remainder consisted primarily of the glucuronide conjugate of fosinopril diacid. Since fosinopril diacid is not biotransformed after intravenous administration, fosinopril (the prodrug) may actually be the substrate for the glucuronide and para-hydroxy metabolites. In rats, the para-hydroxy metabolite of fosinopril diacid is as potent an inhibitor of ACE as fosinopril diacid. As expected, the glucuronide conjugate of fosinopril diacid is devoid of ACE inhibitory activity.

After single and repeated doses, areas under serum concentration time curves (AUC) and peak concentrations (C_{max}) were directly proportional to the dose of fosinopril. The time to reach C_{max} (T_{max}) was independent of dose, achieved in approximately three hours, and consistent with peak inhibition of the angiotensin I pressor response three to six hours following the dose.

Excretion

In healthy subjects, the terminal elimination half-life ($t_{1/2}$) of an intravenous dose of fosinopril diacid was approximately 12 hours. In patients with heart failure, the effective $t_{1/2}$ was 14 hours. In hypertensive patients with normal renal and hepatic function, who received repeated doses of fosinopril, the effective $t_{1/2}$ for accumulation of fosinopril diacid averaged 11.5 hours. Fosinopril diacid is highly protein bound (greater than or equal to 95%), has a relatively small volume of distribution, and negligible binding to cellular components in blood.

Special Populations

Impaired renal function. In patients with renal insufficiency (creatinine clearance < 80 mL/minute/1.73 m2), the pharmacokinetic alterations shown in Table 2 were noted in comparison with normals.

Table 2: Pharmacokinetic alterations in patients with renal insufficiency.

Intravenous fosinopril diacid	Normal (6)	Mild (5)	Moderate (6)	Severe (5)

Total clearance (mL/minute)	25.8	13.7	13.3	14.3
Renal clearance (mL/minute)	10.5	5.1	2.8	2.2
Non-renal clearance (mL/minute)	15.3	8.6	10.6	12.1
120 hour urinary excretion (% dose)	41	41	21	15
120 hour faecal excretion (% dose)	43	44	67	61
Area under curve (ng.hour/mL)	5,133	9,747	9,380	8,401

Absorption, bioavailability and protein binding were not appreciably altered; in the quoted trial, nonrenal excretion of intravenous fosinopril diacid did not increase in absolute terms, however, the increased faecal excretion of the active compound partially compensated for the reduced renal clearance even in patients with endstage renal failure (creatinine clearance < 10 mL/minute/1.73 m2). Therefore, dosage adjustment during the initial stages of treatment will depend on blood pressure response. The initial dose should be 5 to 10 mg. (See 4.2 DOSE AND METHOD OF ADMINISTRATION.)

Clearance of fosinopril diacid by haemodialysis and peritoneal dialysis averages 2 and 7%, respectively, of urea clearances.

Impaired hepatic function. In patients with hepatic insufficiency (alcoholic or biliary cirrhosis), the extent of hydrolysis of fosinopril is not appreciably reduced, although the rate of hydrolysis may be slowed. The apparent total body clearance of fosinopril is approximately one-half of that in patients with normal hepatic function.

Elderly. In clinical studies of fosinopril, no overall differences in effectiveness or safety were observed between elderly (> 65 years old) and younger patients. Additional clinical experience has not identified differences in response between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.

In a pharmacokinetic study comparing elderly (65 to 74 years old) and younger (20 to 35 years old) healthy volunteers, there were no significant differences in pharmacokinetic parameters of fosinopril diacid.

Studies in animals indicate that fosinopril and fosinopril diacid do not cross the blood-brain barrier.

Lactation. In lactating women, bioavailability parameters (AUC, C_{max} and T_{max}) for fosinopril diacid were similar to healthy males. Fosinopril diacid was detectable but not quantifiable in breast milk.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Neither fosinopril sodium nor the active fosinopril diacid was mutagenic in the Ames microbial mutagen test, the mouse lymphoma forward mutation assay, or a mitotic gene conversion assay. Fosinopril was also not genotoxic in a mouse micronucleus test in vivo and a mouse bone marrow cytogenetic assay in vivo.

Carcinogenicity

At least one other ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential to cause this effect with other ACE inhibitors in humans is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign.

In two year studies involving both mice and rats at doses up to 400 mg/kg daily, there was no evidence of a carcinogenic effect.

In the Chinese hamster ovary cell cytogenic assay, fosinopril increased the frequency of chromosomal aberrations when tested without metabolic activation at a concentration that was toxic to the cells. However, there was no increase in chromosomal aberrations at lower drug concentrations without metabolic activation or at any concentration with metabolic activation.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain lactose monohydrate, microcrystalline cellulose, crospovidone, povidone and glyceryl behenate.

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 moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Fosipril 10 Blister packs (Al/Al) of 30.

Fosipril 20 Blister packs (Al/Al) of 30.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

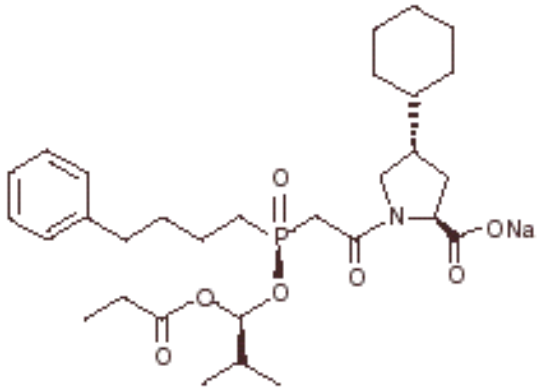
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Fosipril is the sodium salt of fosinopril, the ester prodrug of a long acting angiotensin converting enzyme (ACE) inhibitor, fosinopril diacid. Fosinopril sodium is a white to off-white crystalline powder and is freely soluble in water and methanol, sparingly soluble in ethanol, practically insoluble in ethyl acetate and acetone.

Chemical structure

Fosinopril sodium. The chemical name of fosinopril sodium is [1[S*(R*), 2α, 4β]-4-cyclohexyl-1-[[[2-methyl-1-(-oxopropoxy)propoxy](4-phenylbutyl) phosphinyl]acetyl]-L-proline sodium salt. Its structural formula is:



$C_{30}H_{45}NNaO_7P$ Molecular weight: 585.65

CAS number

CAS: 88889-14-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

22 October 2007.

10 DATE OF REVISION

17 January 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of subheading Anaphylactoid and Possibly Related Reactions and Precaution hyperkalaemia updated to include increase in serum potassium caused by other medicines.
4.5	Hyperkalaemia updated to include increase in serum potassium caused by other medicines.
4.7	Updated to include adverse events may interfere with ability to drive or operate machines.
4.8	Minor editorial change in table 1