SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fosinopril Sodium 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of Fosinopril sodium

Excipient(s) with known effect: Each tablet contains 118mg lactose monohydrate
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, circular, flat, uncoated 8mm tablets marked 'FL 10'.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hypertension:
Fosinopril Sodium 10mg Tablets are indicated in the treatment of hypertension. Fosinopril Sodium 10mg Tablets may be used alone as initial therapy or in combination with other antihypertensive agents. The antihypertensive effects of Fosinopril Sodium 10mg Tablets and diuretics used concomitantly are approximately additive.

Heart Failure:
Fosinopril Sodium 10mg Tablets are indicated for the treatment of heart failure in combination with a non-potassium sparing diuretic and where appropriate, digitalis (see section 4.3, 4.4, 4.5, and 5.1). In these patients, Fosinopril Sodium 10mg Tablets improve symptoms and exercise tolerance, reduce severity of heart failure and decrease the frequency of hospitalisation for heart failure.

4.2 Posology and method of administration

Posology

Fosinopril sodium should be administered orally in a single daily dose. As with all other medicinal products taken once daily, it should be taken at approximately the same time each day. The absorption of fosinopril sodium is not affected by food. The usual initial 10 mg dose has not been studied in patients with severe heart failure NYHA IV and in patients over 75 years treated for heart failure (see section 4.4). The maintenance dose should be individualised according to patient profile and blood pressure response (see section 4.4). Hypertension Fosinopril sodium may be used as a monotherapy or in combination with other classes of antihypertensive medicinal products (see sections 4.3, 4.4, 4.5 and 5.1).

Hypertensive patients not being treated with diuretics:
Starting dose The initial recommended dose is 10 mg once a day. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. The initiation of treatment should take place under medical supervision.

Maintenance dose
The usual daily dose is 10 mg to a maximum of 40 mg administered in a single dose. In general if the desired therapeutic effect cannot be achieved in a period of 3 to 4 weeks on a certain dose level, the dose can be further increased.

Hypertensive patients being treated with concomitant diuretic therapy:
Symptomatic hypotension may occur following initiation of therapy with fosinopril sodium. This is more likely in patients who are being treated currently with diuretics, especially in patients with heart failure, elderly patients (over 75 years) and patients with renal dysfunction. Caution is recommended therefore, since these patients may be volume and/or salt depleted. If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with fosinopril sodium. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with fosinopril sodium should be initiated with a 10 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of fosinopril sodium should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see sections 4.4 and 4.5). When treatment is initiated in a patient already taking diuretics, it is recommended that the treatment with fosinopril sodium is started under medical supervision for several hours and until blood pressure is stabilised.

Special populations

<u>Heart Failure:</u>
The recommended initial dose is 10mg once daily, initiated under close medical supervision. If the initial dose is well tolerated patients should then be titrated to a dose of up to 40mg once daily. The appearance of hypotension after the initial dose should not preclude careful dose titration of Fosinopril Sodium 10mg Tablets, following effective management of the hypotension.

Fosinopril Sodium 10mg Tablets should be used in addition to diuretics and digitalis where appropriate.

Heart Failure - High Risk Patients:
It is recommended that treatment is initiated in hospital for patients with severe cardiac failure (NYHA IV) and those at particular risk of first dose hypotension, i.e. patients on multiple or high dose diuretics (e.g.> 80mg furosemide), patients with hypovolaemia, hyponatraemia (serum sodium < 130 meq/l), pre-existing hypotension (systolic blood pressure <90 mmHg), patients with unstable cardiac failure and those on high-dose vasodilator therapy. Renal function and serum potassium should be monitored (see section 4.4).

Paediatric population:
Use in this age group is not recommended. There is limited clinical trial experience of the use of fosinopril in hypertensive children aged 6 years and above (see section 5.1, 5.2 and 4.8). The optimum dosage has not been determined in children of any age. An appropriate dose strength is not available for children weighing less than 50kg.

Elderly
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 fosinoprilat have been found compared with younger subjects.

Impaired hepatic function
Treatment should be initiated at a dose of 10mg. Although the rate of hydrolysis 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 fosinoprilat with compensatory increase in renal excretion.

Renal impairment
Treatment should be initiated at a dose of 10mg, however caution is advised especially with a GFR of less than 10 ml/min. Depending on the response, the dose should then be titrated to achieve the desired therapeutic effect.

Absorption, bioavailability, protein binding, biotransformation and metabolism are not appreciably altered by reduced renal function. In patients with impaired renal function, the total body clearance of fosinoprilat is approximately 50% slower than that in patients with normal renal function. However, since hepatobiliary elimination compensates at least partially for diminished renal elimination, the body clearance of fosinoprilat is not appreciably different over a wide range of renal insufficiency (creatinine clearances ranging from <10 to 80 ml/min/1.73m^2, i.e. including end-stage renal failure).

Neither haemodialysis nor peritoneal dialysis is effective in clearing fosinoprilat. Peritoneal clearance is insignificant, ranging from 0.07 to 0.23ml per minute. Similarly haemodialysis for four hours clears only approximately

1.5% of the administered dose. This corresponds to 7% and 2% respectively, of urea clearance. Hence no dose adjustment is necessary to correct for drug loss during these procedures.

NB Fosinopril is NOT licensed for use in acute myocardial infarction.

Method of administration:

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance, other angiotencin-converting enzyme (ACE) inhibitors or to any of the excipients listed in section 6.1.
- History of angioneurotic oedema
- History of angioedema associated with previous ACE inhibitor therapy
- Renal artery stenosis (bilateral or unilateral in single kidney), and
- Cardiogenic shock.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- The concomitant use of fosinopril with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73m^2). (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Fosinopril sodium must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

WARNING

Hypotension:
Fosinopril sodium has been rarely associated with hypotension in uncomplicated hypertensive patients. As with other ACE inhibitors, symptomatic hypotension is most likely to occur in salt/volume depleted patients such as those treated vigorously with diuretics, those patients undergoing renal dialysis, dietary salt restriction, diarrhoea or vomiting, or has severe renin-dependent hypertension (see sections 4.5 and 4.8). 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 replenishment of salt and/or volume.

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 azotemia and, rarely, with acute renal failure and death. In such patients, fosinopril sodium therapy should be started under close medical supervision; they should be followed closely for the first 2

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 hyponatremic.

Hypotension is not *per se* a reason to discontinue fosinopril. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilizes within a week or two, and generally returns to pretreatment levels without a decrease in therapeutic efficacy.

The safety of an initial 10mg dose has not been studied in patients with severe heart failure NYHA IV. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9mg/ml (0.9%) solution.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other angiotensin-converting enzyme (ACE) inhibitors, fosinopril sodium should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Impaired renal function:
In cases of renal impairment, the initial dosage of fosinopril sodium need not be adjusted. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients. In hypertensive patients with renal artery stenosis in one or both kidneys, increases in blood urea nitrogen and serum creatinine may occur during treatment with an ACE inhibitor. These increases are usually reversible upon discontinuation of therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration.

Some hypertensive patients with no apparent pre-existing renal vascular disease develop increases in blood urea nitrogen and serum creatinine, usually minor or transient, when fosinopril is given concomitantly with a diuretic. This effect is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of fosinopril sodium may be required.

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

Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of therapy with fosinopril sodium.

Proteinuria
In patients with pre-existing renal impairment proteinuria may occur in rare cases. In clinically relevant proteinuria (greater than 1 g/day) Fosinopril should only be used after a very critical benefit/risk evaluation and with regular monitoring of the clinical and laboratory chemical parameters.

Anaphylactoid reactions during desensitization:
Two patients undergoing desensitizing 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 desensitizations procedures.

Anaphylactoid reactions during high-flux dialysis/lipoprotein apheresis membrane exposure:
Anaphylactoid reactions have been reported in patients hemodialyzed with highflux dialysis membranes while on therapy with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Hypersensitivity/angioedema:
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of fosinopril sodium. Treatment with fosinopril sodium must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section 4.3).

Head and neck angioedema:
Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors. If such

symptoms occur during treatment with Fosinopril Sodium 10mg Tablets, therapy should be discontinued.
Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline (epinephrine) and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

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 abdominal CT scan 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.

Hepatic failure:
Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Fosinopril sodium Tablets who develop jaundice or marked elevations of hepatic enzymes should discontinue Fosinopril sodium Tablets and receive appropriate medical follow-up.

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

Hyperkalemia/Serum potassium:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including fosinopril. ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section

4.5).Patients at risk for the development of hyperkalemia include those with renal insufficiency, diabetes mellitus, hypoaldosteronism or those using concomitant potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs associated with increases in serum potassium (e.g, heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Neutropenia/agranulocytosis

Neutropenia / agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Fosinopril sodium should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If fosinopril sodium is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Surgery/anaesthesia:

ACE inhibitors may augment the hypotensive effects of anaesthetics and analgesics. If hypotension occurs in patients undergoing surgery/anaesthesia and concomitantly receiving ACE inhibitors, it can usually be corrected by intravenous administration of fluid.

Paediatric population

Safety and effectiveness in children have not been established.

Geriatric use

Among patients who received fosinopril sodium in clinical studies, overall differences in efficacy or safety were not observed between older patients (65 years or older) and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.

PRECAUTIONS

Cough:

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

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 an ACE inhibitor (see section 4.5)

Pre-treatment assessment of renal function:
Evaluation of the hypertensive patient should include assessment of renal function prior to initiation of therapy and during treatment where appropriate.

Dialysis:
See section 4.2 regarding use of fosinopril in patients receiving haemodialysis or peritoneal dialysis.

Aortic stenosis, mitral stenosis and hypertrophic cardiomyopathy:
In severe cases of these conditions where patients have fixed cardiac output, fosinopril may cause a large fall in blood pressure as such patients cannot compensate for the reduction in peripheral resistance with an increase in cardiac output.

Ethnic factors:
ACE inhibitors cause a higher rate of angioedema in black than in non-black patients. When fosinopril is given as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Fetal/Neonatal morbidity and mortality:
When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus.

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 sections 4.5 and 5.1). 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 diabetic nephropathy.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

Antacids:

Antacids (ie, aluminum hydroxide, magnesium hydroxide, and simethicone) may impair absorption of fosinopril. Administration of Fosinopril Sodium 10mg Tablets and antacids should be separated by at least 2 hours.

NSAIDs:
Non-steroidal anti-inflammatory drugs and more than 3g/day aspirin may interfere with the antihypertensive effect. However, the concomitant use of fosinopril and NSAIDs (including aspirin) is not associated with an increase in clinically significant adverse reactions. As with any ACE inhibitor, in some patients with compromised renal function the co-administration of fosinopril and NSAIDs may result in a further deterioration of renal function.

Co-trimoxazole (trimethoprim/sulfamethoxazole)
Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Tricyclic antidepressants / Antipsychotics / Anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates
Fosinopril sodium may be used concomitantly with acetylsalicylic acid (at cardiological doses), thrombolytics, beta-blockers and/or nitrates.

Immunosuppressants, cytostatics, systemic corticosteroids or procainamide, allopurinol
The combination of fosinopril sodium with immunosuppressant medicinal products and/or medicinal products that can cause leucopenia should be avoided.

Alcohol
Alcohol enhances the hypotensive effect of fosinopril sodium.

Lithium:
Increased serum lithium levels and risk of lithium toxicity have been reported in patients receiving ACE inhibitors concomitantly with lithium. Fosinopril sodium and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

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 nonsteroidal anti-inflammatory agents (eg, aspirin) may have a similar effect.

Diuretics:
Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restrictions or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of fosinopril sodium (see section 4.4).

Other Anti-Hypertensive Agents:
Combination with other anti-hypertensive agents such as beta blockers, methyldopa, calcium antagonists, and diuretics may increase the anti-hypertensive effect. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosteronesystem (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 sections 4.3, 4.4 and 5.1).

Immunosuppressants:
Concomitant use of fosinopril with immunosuppressants (e.g. azathioprine) may increase the risk of leucopenia developing.

<u>Combinations not recommended:</u>

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes (see section 4.4, Hyperkalaemia)
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with fosinopril sodium. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when fosinopril sodium is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of fosinopril sodium with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes or other medicinal products associated with increases in serum potassium (e.g. heparin). The use of the above-mentioned products, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If fosinopril sodium is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

Other Drugs:

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

In pharmacokinetic studies with nifedipine, propranolol, cimetidine, metoclopramide and propantheline the bioavailability of fosinoprilat was not altered by coadministration of fosinopril with any one of these drugs.

Fosinopril has been used concomitantly with paracetamol, antihistamines, lipid-lowering agents or oestrogen without evidence of clinically important adverse events.

Interference with serological testing:
Fosinopril Sodium 10mg Tablets may cause a false low measurement of serum digoxin levels with assays using the charcoal absorption method for digoxin. Other kits which use the antibody coated-tube method may be used. Therapy with fosinopril sodium should be interrupted for a few days before carrying out tests for parathyroid function.

4.6 Fertility, pregnancy and lactation

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4). Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3.) Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Fosinoprilat, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Breast-feeding
Because only very limited information is available regarding the use of Fosinopril Tablets during breastfeeding, Fosinopril tablets is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on ability to drive and use machines

Whilst fosinopril is not expected to directly affect performance, it can cause adverse effects such as dizziness, vertigo or hypotension which may interfere with driving or use of machines.

This occurs especially at the start of treatment, when increasing the dosage, when changing over from other preparations and during concomitant use of alcohol, depending on the individual’s susceptibility.

Patients should make sure they are not affected before driving or operating machinery.

4.8 Undesirable effects

In the patients treated with Fosinopril sodium Tablets, the adverse effects were in general mild and transient.

Very common: ≥1/10
Common: ≥1/100 and <1/10
Uncommon: ≥1/1000 and <1/100
Rare: ≥1/10 000 and <1/1000
Very rare: <1/10000 including isolated cases
Not Known: (cannot be estimated from the available data)

Infections and infestations
Common: Upper respiratory infection, pharyngitis, rhinitis, viral infection
Uncommon: Sinusitis, tracheobronchitis
Rare: Pneumonia
Not known: Laryngitis

Blood and lymphatic system disorders
Uncommon: Transient decrease in haemoglobin, decrease in haematocrit
Rare: Transient anaemia, eosinophilia, leucopenia, lymphadenopathy, neutropenia, thrombocytopenia
Very rare: Agranulocytosis

Metabolism and nutrition disorders
Uncommon: Decreased appetite, gout, hyperkalaemia
Not Known: Appetite disorder, weight fluctuation

Psychiatric disorders
Common: Mood altered, sleep disorder
Uncommon: Depression, confusion
Not Known: abnormal behaviour

Nervous system disorders
Common: Dizziness, headache, paraesthesia
Uncommon: Syncope, cerebral infarction, somnolence, tremor, stroke, taste disturbances, sleep disturbance
Rare: Dysphasia, memory disturbances, disorientation
Not Known: balance disorder

Eye disorders
Common: Eye disorder, visual disturbances

Ear and labyrinth disorders
Uncommon: Ear pain, tinnitus, vertigo

Cardiac disorders
Common: Tachycardia, arrhythmia, palpitations, angina pectoris

Uncommon: Myocardial infarction or cerebrovascular accident, cardiac arrest, rhythm disturbances, conduction disturbances
Not known: cardio-respiratory arrest,

Vascular disorders
Common: Hypotension, orthostatic hypotension
Uncommon: Shock, hypertension, transitory ischaemia
Rare: Flush, haemorrhage, peripheral vascular disease
Not known: Hypertensive crisis

Respiratory, thoracic and mediastinal disorders
Common: Cough
Uncommon: Dyspnoea
Rare: Bronchospasm, epistaxis, pulmonary congestion
Not known: Dysphonia, pleuritic pain

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, abdominal pain, dyspepsia, dysgeusia
Uncommon: Constipation, dry mouth, flatulence
Rare: Oral lesions, pancreatitis, swollen tongue, abdominal distension, dysphagia
Very rare: Intestinal angioedema, (sub) ileus

Hepatobiliary disorders
Rare: Hepatitis
Very rare: Hepatic failure

Skin and subcutaneous tissue disorders
Common: Rash, angioedema, dermatitis
Uncommon: Hyperhidrosis, pruritus, urticaria
Rare: Ecchymosis

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Musculoskeletal and connective tissue disorders
Common: Musuloskeletal pain, myalgia
Rare: Arthritis

Renal and urinary disorders
Common: Micturition disorder
Uncommon: Renal failure, proteinuria
Rare: Prostatic disorders
Very rare: acute renal failure

Reproductive and breast disorders
Common: Sexual dysfunction

General disorders and administration site conditions
Common: Fatigue, chest pain (non-cardiac), oedema, asthenia, weakness
Uncommon: Fever, peripheral oedema, sudden death, thoracic pain
Rare: Weakness in one extremity
Not known: Pain pyrexia

Investigations
Common: Increase in alkaline phosphatase, increase in bilirubin, increase in LDH, increase in transaminases
Uncommon: Weight increase, increases in blood urea, increases in serum creatinine
Rare: Slight increase in haemoglobin, hyponatremia
Not known: Liver function test abnormal

In the clinical studies performed with fosinopril, the incidence of adverse effects did not differ between elderly (more than 65 years of age) and younger patients.

Hypotension or syncope was a cause for discontinuation of therapy in 0.3% of patients.

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

Paediatric population
Safety data in the paediatric population receiving fosinopril is still limited, only a short-term exposure has been evaluated. In a randomized clinical trial of 253 children and adolescents aged 6 to 16 years, the following adverse events occurred in the 4 week double blind phase: headache (13.9%), hypotension (4.8%), cough (3.6%) and hyperkalaemia (3.6%), elevated serum creatinine levels (9.2%) and elevated serum creatinine kinase levels (2.9%). Different from the adults are this elevated CK reported in this trial (even transient and with no clinical symptoms). The long-term effects of fosinopril on growth, puberty, and general development have not been studied.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
The symptoms of overdosage may include severe hypotension, circulatory shock, electrolyte disturbance, renal failure, hyperventilation tachycardia,

palpitations, bradycardia, dizziness, anxiety and cough. The recommended treatment of overdose is intravenous infusion of normal saline solution.

After ingestion of an overdose the patient should be kept under very close supervision preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Therapeutic measures depend on the nature and severity of the symptoms. Measures to prevent absorption such as gastric lavage, administration of adsorbents and sodium sulfate within 30 minutes after intake and hasten elimination should be applied if ingestion is recent. If severe hypotension occurs the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II (if available) may be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of high-flux polyacrylonitrile dialysis membrane should be avoided. Serum electrolytes and creatinine should be monitored frequently. The use of a pacemaker may be considered.

Management
Treatment overview:

- A. ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.
- B. HYPOTENSION: Infuse 10 to 20 mL/kg isotonic fluid, place in Trendelenburg position. If hypotension persists, administer dopamine (5 to 20 mcg/kg/min) or noradrenaline (norepinephrine) (0.1 to 0.2 mcg/kg/min), titrate to desired response.
    - 1. Angiotensin infusion at doses ranging from 8.5 to 18 mcg/minute has been successful in reversing hypotension in patients who did not respond to volume and pressor infusions.
    - 2. Naloxone has also been effective in some patients with hypotension.
- C. ANGIOEDEMA - Administer antihistamines and corticosteroids. Monitor airway carefully and administer oxygen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: CO9A A09
Pharmacotherapeutic group: ACE Inhibitors, plain.

Mechanism of action:
Fosinopril is the pro-drug (ester) of the long acting active ACE inhibitor fosinoprilat. After oral administration fosinopril is quickly and fully metabolised to the active fosinoprilat. Fosinopril contains a phosphinic group capable of a specific binding to the active site of the angiotensin converting enzyme, preventing the conversion of angiotensin I in angiotensin II. The

reduction in angiotensin II leads to a vasoconstriction reduction and a decrease in aldosterone secretion, which might induce a slight increase in serum potassium and a loss of sodium and fluid.
ACE inhibition also interferes with bradykinin degradation, a potent vasodepressant, contributing to the antihypertensive effect; fosinopril presents a therapeutic action in hypertensive patients with renin low levels.

In patients with cardiac failure, it is assumed that Fosinopril beneficial effects are mainly resultant of a suppression of the renin-angiotensin-aldosterone system; ACE inhibition produces a reduction in pre-load and post-load.

Pharmacodynamic effects
Administration of fosinopril sodium to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate. In hypertension, fosinopril sodium reduces blood pressure within one hour of administration, the maximum effect being observed within 3-6 hours. With the usual daily dosage, the anti-hypertensive effect lasts for 24 hours. In some patients receiving lower dosages the effect may be reduced at the end of the dosage interval. The orthostatic effects and tachycardia are rare but might occur in patients with salt depletion or in hypovolemia (see section 4.4). In some patients the development of optimal blood pressure reduction may require 3-4 weeks of therapy. Fosinopril sodium and thiazide diuretics have additive effects. In heart failure, fosinopril sodium improves symptoms and exercise tolerance and reduces the severity of and frequency of hospitalisation due to cardiac failure. In a study of 8 cirrhotic patients, fosinopril 20 mg/day for one month did not change hepatic (alanine transferase, gamma-glutamyl-transpeptidase, galactose clearance test and antipyrine clearance test) or renal functions.
Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early

because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population
Reduction of blood pressure with low (0.1mg/kg), medium (0.3mg/kg) and high (0.6mg/kg) target doses of once-daily fosinopril was evaluated in a randomised double-blind study of 252 children and adolescents aged 6 to 16 years of age with hypertension or high-normal blood pressure. At the end of the four weeks of treatment, the mean reduction from baseline in trough systolic blood pressure was similar for children treated with low, medium and high dose fosinopril. No dosage response relationship was demonstrated between the three doses. The optimum dosage has not been determined in children of any age. An appropriate dose strength is not available for children weighting less than 50kg.

5.2 Pharmacokinetic properties

Absorption
After oral administration, the extension of the absorption of fosinopril averages 30% to 40%. The absorption of fosinopril is not affected by the presence of food in gastrointestinal tract, however the speed of the absorption might be reduced. Rapid and complete hydrolysis to active fosinoprilat occurs in the gastrointestinal mucosa and liver. The time to reach the maximum plasma concentration is approximately three hours and is independent of administered dose. After multiple or single doses, the pharmacokinetic parameters (C_{max}, AUC) are directly proportional to the fosinopril dose that has been taken.

Distribution
Fosinoprilat is protein bound (> 95%), but has a negligible binding to blood cellular components.

Biotransformation
One hour after oral administration of fosinopril sodium, less than 1% fosinopril in plasma remains unchanged; 75% is present as active fosinoprilat, 15-20% as fosinoprilat glucuronide (inactive), and the remainder (~5%) as the 4-hydroxy metabolite of fosinoprilat (active).

Elimination
After intravenous administration, the elimination of fosinopril is by both hepatic and renal routes. In hypertensive patients that receive repeated doses of fosinopril and have normal renal and hepatic functions, the fosinoprilat elimination half-life is 11.5 hours, being of 14 hours in patients with cardiac failure.

Other special populations

Patients with renal impairment
In patients with renal failure (creatinine clearance < 80 ml/min/1,73 m^2), the total fosinoprilat body clearance is approximately half of that observed in patients with normal renal function, while no significant changes are seen in the absorption, the bioavailability and the plasma protein binding. The fosinoprilat clearance does not vary according with the degree of renal failure; the reduction in renal elimination is compensated by the increase in hepato-biliary elimination. A slight increase in AUC values (less than the double of normal values) has been observed in patients with several degrees of renal failure, including terminal renal failure (creatinine clearance < 10 ml/min/1.73 m^2).

Patients with hepatic impairment
In patients with hepatic failure (alcoholism or biliary cirrhosis), the fosinopril hydrolysis is not significantly reduced, although the rate of the hydrolysis might be reduced; the total fosinoprilat clearance is almost half of the clearance observed in patients with normal hepatic function.

Paediatric population
Limited pharmacokinetic data in children and adolescents were provided by a single-dose pharmacokinetic study in 19 hypertensive patients 6 to 16 years of age who received 0.3mg/kg of a solution of fosinopril.

Whether AUC and Cmax values of fosinoprilat (active form of fosinopril) in children from 6 to 16 years of age were comparable to those seen in adults receiving 20mg of fosinopril as a solution, has to be demonstrated.

The terminal elimination half-life for fosinoprilat was 11-13 hours and similar at all stages studied.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that fosinopril has no negative effects on fertility and reproductive performance in rats, and is not teratogenic. ACE inhibitors, as a class, when given in the second or third trimester, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal reninangiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrient delivery to the foetus. In a study in which female rats were dosed with fosinopril prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The substance has been shown to cross the placenta and is secreted in milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Also contains:

Lactose monohydrate
Pregelatinised starch
Croscarmellose sodium
Microcrystalline cellulose
Glycerol dibehenate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium-aluminium blisters

Each carton will contain either 7, 10, 14, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98, 100* tablets.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0582

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/09/2018

10 DATE OF REVISION OF THE TEXT

16/12/2020