

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fosinopril Medis 10 mg tablets

Fosinopril Medis 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg fosinopril sodium.

Excipient with known effect:

Each tablet contains 118 mg lactose monohydrate.

Each tablet contains 20 mg fosinopril sodium.

Excipient with known effect:

Each tablet contains 108 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Fosinopril Medis 10 mg tablets:

White to off-white round tablets, imprinted "FL10". Diameter 8 mm.

Fosinopril Medis 20 mg tablets:

White to off-white round tablets, imprinted "FL20". Diameter 8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension.

Treatment of symptomatic heart failure.

4.2 Posology and method of administration

Posology

The 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. 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 section 4.4 and section 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.

Heart failure

In patients with symptomatic heart failure, fosinopril sodium should be used as adjunctive therapy to diuretics and, where appropriate, digitalis. The recommended initial dose is 10 mg 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 40 mg once daily based on clinical response. The appearance of hypotension after the initial dose should not preclude careful dose titration of fosinopril sodium, following effective management of the hypotension.

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with fosinopril sodium. The treating physician may consider to give an initial dose of 5 mg to determine the hypotensive effect in high risk patients. The dose should subsequently be adjusted until optimal response is achieved. Renal function and serum potassium should be monitored (see section 4.4).

Special populations

Patients with renal insufficiency

An initial dose of 10 mg per day is recommended, however caution is advised especially with a GFR of less than 10 ml/min.

Patients with impaired liver function

An initial dose of 10 mg per day is recommended, however caution is advised. 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.

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 50 kg.

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.

Method of administration

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.

4.3 Contraindications

- Hypersensitivity to the active substance, any other angiotensin-converting enzyme (ACE) inhibitor or to any of the excipients listed in section 6.1.
- History of angioedema associated with previous ACE inhibitor therapy,
- Hereditary or idiopathic angioneurotic oedema,
- Second and third trimester of pregnancy (see sections 4.4 and 4.6)
- The concomitant use of Fosinopril Medis with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment ($\text{GFR} < 60 \text{ ml/min/1.73 m}^2$) (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

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.

Hypotension

Fosinopril sodium has been rarely associated with hypotension in uncomplicated hypertensive patients. In hypertensive patients receiving fosinopril sodium, symptomatic hypotension is most likely to occur if the patient has been salt/volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 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 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. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored; they should be followed closely for the first 2 weeks of treatment and whenever the dose of fosinopril or diuretic is increased. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9 %) solution.

A transient hypotensive reaction is not a contraindication for the continued administration of fosinopril sodium. After the effective blood volume and blood pressure have been restored, treatment with fosinopril sodium can be continued, but a reduced dose could be considered.

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.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with fosinopril sodium. This effect is anticipated and is not usually a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of fosinopril sodium may be necessary.

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 stabilises within a week or two, and generally returns to pretreatment levels without a decrease in therapeutic efficacy.

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.

Renal function impairment

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 care for these patients.

In patients with heart failure, hypotension in response to initiation of ACE inhibitor therapy may lead to further deterioration of renal function. Acute, usually reversible, renal failure has been reported in this situation. Dosage reduction and/or discontinuation of the ACE inhibitor 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.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea nitrogen and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 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. 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.

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

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.

Patients after kidney transplantation

Since there is no experience with the use of fosinopril sodium in patients who have recently had a kidney transplant, the administration of fosinopril sodium is not recommended in this patient group.

Hypersensitivity/angioedema

Angioedema has been seen in patients treated with ACE inhibitors, including fosinopril sodium. This may occur at any time during therapy. In such cases, fosinopril sodium should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. 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 be insufficient.

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, which can be fatal. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline 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.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of fosinopril; some cases required medical therapy.

ACE inhibitors cause a higher rate of angioedema in Black patients than in non-Black patients.

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).

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. Treatment with fosinopril 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.

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.

Anaphylactoid reactions in haemodialysis patients

Anaphylactoid reactions have been reported in patients haemodialysed with high flux dialysis membranes (e.g. AN 69) while on therapy with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Rarely, patients receiving ACE inhibitors during LDL apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld but they reappeared upon inadvertent re-administration of the medicinal product. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Hepatic failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis 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 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 biliary cirrhosis, the apparent total body clearance of fosinoprilat was decreased and the plasma AUC approximately doubled.

Neutropenia/agranulocytosis

Neutropenia/agranulocytosis, bone marrow depression, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. Agranulocytosis and bone marrow depression occur more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. 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 count is advised and patients should be instructed to report any sign of infection.

Race

As with other ACE inhibitors, fosinopril sodium may be less effective in lowering blood pressure in Black patients than in non-Blacks, possibly because of a higher prevalence of low-renin states in the Black hypertensive population.

Cough

Cough has been reported with the use of ACE inhibitors, including fosinopril. 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.

Surgery/anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, fosinopril sodium may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Serum potassium

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including fosinopril sodium. Patients at risk for the development of hyperkalaemia include those with renal insufficiency and diabetes mellitus.

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).

If concomitant use of any other of the above-mentioned products is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

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)

Lithium

The combination of lithium and fosinopril sodium is generally not recommended (see section 4.5).

Paediatric population

Safety and effectiveness in children have not been established (see sections 4.2, 4.8, 5.1 and 5.2).

Elderly

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.

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 anti-hypertensive 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).

Excipient(s)

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics

When a diuretic is added to the therapy of a patient receiving fosinopril sodium, the antihypertensive effect is usually additive.

Patients already 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 an excessive reduction of blood pressure usually within the first hour after receiving the initial dose of fosinopril sodium. The possibility of symptomatic hypotension with fosinopril sodium can be minimised by discontinuing the diuretic prior to initiation of treatment with fosinopril sodium (see section 4.4 and section 4.2). The possibility of symptomatic hypotension following administration of fosinopril sodium can be minimized by discontinuing the diuretic 2 to 3 days before initiating treatment with fosinopril sodium.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

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 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.

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.

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).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Fosinopril sodium and lithium should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended (see section 4.4).

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid $\geq 3\text{g/day}$

Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated. Therefore, concomitant treatment with NSAIDs and ACE inhibitors in this population should be used with caution, and patients should be adequately hydrated. The renal function should be monitored regularly.

It has been reported that indomethacin may reduce the antihypertensive effect of other ACE inhibitors, especially in cases of low renin hypertension.

Other antihypertensive agents

Combination with other antihypertensive agents such as beta-blockers, methyl dopa, calcium antagonists, and diuretics may increase the anti-hypertensive efficacy.

Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

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 sections 4.3, 4.4 and 5.1).

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 a 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.

Antacids and carminatives

Antacids (e.g. aluminium hydroxide, magnesium hydroxide) and the carminative simethicone may impair absorption of fosinopril sodium. Therefore, if concomitant administration of these agents is indicated, dosing should be separated by at least 2 hours.

Laboratory interactions

Fosinopril sodium may cause a false low measurement of serum digoxin levels with assays using the charcoal absorption method. Other kits, which utilize the antibody coated-tube method, may be used instead.

It is recommended to suspend the treatment with fosinopril sodium a few days before performing parathyroid tests.

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 inhibitors 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).

Breast-feeding

Because only very limited information is available regarding the use of fosinopril during breastfeeding, fosinopril 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

No studies on the effects on the ability to drive and use machines have been performed.

Although fosinopril sodium is not expected to affect directly, adverse reactions such as hypotension, dizziness and vertigo 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.

4.8 Undesirable effects

Tabulated list of adverse reactions

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

System organ class	Common ($\geq 1/100$, $< 1/10$)	Uncommon ($\geq 1/1,000$, $< 1/100$)	Rare ($\geq 1/10,000$, $< 1/1,000$)	Very rare ($< 1/10,000$)	Not known (cannot be estimated from the available data)
Infections and infestations	Upper respiratory tract infection, pharyngitis, rhinitis, viral infection	Sinusitis, tracheobronchitis	Laryngitis/hoarseness, pneumonia		
Blood and lymphatic system disorders		Decrease in haematocrit	Transient anaemia, eosinophilia, leukopenia, lymphadenopathy, neutropenia, thrombocytopenia	Agranulocytosis	
Immune system disorders					Hypersensitivity reactions (see section 4.4)
Metabolism and nutrition disorders		Decreased appetite, weight increase, gout, hyperkalaemia			Appetite disorder, weight fluctuation
Psychiatric disorders	Mood altered, sleep disorder	Depression, abnormal behaviour, confusion			
Nervous system disorders	Dizziness, headache, paraesthesia, dysgeusia	Cerebral infarction, somnolence, stroke, syncope, tremor	Dysphasia, memory disturbances, disorientation		Balance disorder

System organ class	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1.000, < 1/100)	Rare (≥ 1/10.000, < 1/1.000)	Very rare (< 1/10.000)	Not known (cannot be estimated from the available data)
Eye disorders	Eye disorder, visual disturbances				
Ear and labyrinth disorders		Ear ache, tinnitus, vertigo			
Cardiac disorders	Tachycardia, arrhythmia, palpitations, angina pectoris	Myocardial infarction, cardiac arrest, conduction disturbances			Cardio-respiratory arrest
Vascular disorders	Hypotension, orthostatic hypotension	Hypertension, shock, transient ischaemic attack	Flush, haemorrhage, peripheral vascular disease		Hypertensive crisis
Respiratory, thoracic and mediastinal disorders	Cough, sinus disorder	Dyspnoea	Bronchospasm, epistaxis, pulmonary congestion		Dysphonia, pleuritic pain
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain, dyspepsia	Constipation, dry mouth, flatulence	Oral disorder, pancreatitis, swollen tongue, abdominal distension, dysphagia	Intestinal angioedema, (sub) ileus	
Hepatobiliary disorders			Hepatitis	Hepatic failure (see section 4.4)	
Skin and subcutaneous tissue disorders	Rash, angioedema, dermatitis	Hyperhidrosis, pruritus, urticaria	Ecchymosis		
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, myalgia		Arthritis		Muscular weakness
Renal and urinary disorders	Micturition disorder	Renal failure, proteinuria		Acute renal failure	
Reproductive system and breast disorders	Sexual dysfunction	Impotence, gynecomastia	Prostatic disorder		
General disorders and administrative	Chest pain (non-cardiac), asthenia,	Pyrexia, peripheral oedema, thoracic pain	Weakness in one extremity		Pain

System organ class	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1.000, < 1/100)	Rare (≥ 1/10.000, < 1/1.000)	Very rare (< 1/10.000)	Not known (cannot be estimated from the available data)
on site conditions	fatigue, oedema				
Investigations	Increase in alkaline phosphatase, increase in bilirubin, increase in LDH, increase in transaminases	Transient decrease in haemoglobin, increases in blood urea, increases in serum creatinine	Slight increase in haemoglobin, hyponatremia		Liver function test abnormal

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.

During clinical trials with fosinopril sodium, the incidence of adverse events in the elderly (≥ 65 years old) was similar to that of 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 sodium.

Paediatric population

Safety data in the paediatric population receiving fosinopril sodium is still limited, as there was only evaluated a short-term exposure. 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 %), 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 national reporting system listed in [Appendix V](#)

4.9 Overdose

Symptoms

Symptoms associated with overdosage of ACE inhibitors may include severe hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

Therapy

Therapeutic measures depend on the time of administration as well as the type and severity of the symptoms. No specific information is available on the treatment of overdosage with fosinopril sodium; treatment should be symptomatic and supportive. Therapy with fosinopril sodium should be

discontinued and the patient closely monitored. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously. Intensive care may be warranted. In case of hypotension, appropriate countermeasures must be initiated. The patient should be placed in shock position and physiological saline solution should be administered as infusion. In case of bradycardia or severe vagal reactions, atropine should be considered. The use of a pacemaker can be considered in case of therapy-refractory bradycardia. Induction of vomiting, gastric lavage, or administration of adsorbents could be considered, provided recent ingestion of fosinopril sodium.

Fosinopril is poorly removed from the body by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE Inhibitors, plain, ATC code: C09A A09

Mechanism of action

Fosinopril sodium is an ester prodrug of the long-acting ACE inhibitor, fosinoprilat. After oral administration, fosinopril is quickly and fully metabolised to the active fosinoprilat. Fosinopril sodium contains a phosphinic group capable of specific binding to the active site of the peptidyl dipeptidase angiotensin-converting enzyme, preventing the conversion of decapeptide angiotensin I to the octapeptide, angiotensin II. The resulting reduction in angiotensin II levels leads to a reduction in vasoconstriction and a decrease in aldosterone secretion, that might induce a slight increase in serum potassium and a loss of sodium and fluid. Usually, there is no change in renal blood flow or glomerular filtration rate.

ACE inhibition also prevents the degradation of the potent vasodepressor bradykinin, contributing to the antihypertensive effect; fosinopril sodium presents a therapeutic action in hypertensive patients with low renin levels.

In patients with heart failure, it is assumed that the beneficial effects of fosinopril sodium are mainly due to suppression of the renin-angiotensin-aldosterone system; ACE inhibition produces a reduction in pre-load and after-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.

Clinical efficacy and safety

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 (0.1 mg/kg), medium (0.3 mg/kg) and high (0.6 mg/kg) target doses of once daily fosinopril was evaluated in a randomised double-blind study of 253 children and adolescents aged 6-16 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 dose 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 weighing less than 50 kg.

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 rate of absorption might be reduced. Rapid and complete hydrolysis to active fosinoprilat occurs in the gastrointestinal mucosa and liver.

The time to reach C_{max} is independent of dose, achieved in approximately three hours and consistent with peak inhibition of the angiotensin I pressor response 3 to 6 hours following administration. 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 highly protein bound (> 95 %), has a relatively small volume of distribution and negligible binding to cellular components in blood.

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 with normal renal and hepatic function who received repeated doses of fosinopril, the effective $T_{1/2}$ for accumulation of fosinoprilat averaged 11.5 hours. In patients with heart failure, the effective $T_{1/2}$ was 14 hours. The elimination of fosinopril is by both hepatic and renal routes.

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 0.3 mg/kg of a solution of fosinopril.

Whether AUC and C_{max} values of fosinoprilat (active form of fosinopril) in children from 6 to 16 years of age were comparable to those seen in adults receiving 20 mg 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 studies.

Special patient groups

In patients with renal failure (creatinine clearance < 80 ml/min/1.73 m²), the total body clearance of fosinoprilat 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 clearance of fosinoprilat 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 m²).

In patients with hepatic failure (alcoholism or biliary cirrhosis), the fosinopril sodium 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.

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 renin-angiotensin 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

Lactose monohydrate
Croscarmellose sodium
Pregelatinised maize starch
Cellulose, microcrystalline
Glycerol dibehenate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters and unopened tablet containers:

2 years

Tablet containers after opening:
100 days

6.4 Special precautions for storage

Do not store above 25°C.

Blisters: Store in the original package in order to protect from moisture.

Tablet containers (PP): Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Blisters (Al/PVC/PA/Al): 10, 14, 20, 28, 30, 42, 50, 98 and 100 tablets

Tablet container (PP with a lid of LDPE with desiccant): 50, 100, 250 and 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

For RMS:
Teva B.V.
Swensweg 5
Haarlem, 2031GA
The Netherlands

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

For RMS:
10 mg: 19386
20 mg: 19387

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

For RMS:
2005-02-04/2010-02-04

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2025-05-14