1.3.1.1 SUMMARY OF PRODUCT CHARACTERISTICS

Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

[Fosinopril sodium 10 mg, tablets]
[Fosinopril sodium 20 mg, tablets]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 or 20 mg fosinopril sodium.

Excipient:
Each tablet fosinopril sodium 10 mg contains 87 mg of lactose, anhydrous.
Each tablet fosinopril sodium 20 mg contains 174 mg of lactose, anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
The 10 mg tablets are white and shaped like a capsule with indents. On one side they are engraved with the letters “APO” and on the other side with “FOS-10”.
The 20 mg tablets are white and their shape is oval. On one side they are engraved with the letters “APO” and on the other side with “FOS-20”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of hypertension.
- Treatment of symptomatic heart failure.

4.2 Posology and 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.
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.

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. The most common dose is 20 mg 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).

**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.

**Children and adolescents:**
[product name] is not recommended for use in children below 18 years of age due to insufficient data on safety and/or efficacy.

**Use in the 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.
The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water).

4.3 Contraindications

- Hypersensitivity to fosinopril, other ACE inhibitors or one of the excipients of this product
- History of angioedema due to previous treatment with an ACE inhibitor
- Hereditary or idiopathic angioedema
- Second and third trimester of pregnancy (see sections 4.4 and 4.6)

4.4 Special warnings and precautions for use

Symptomatic Hypotension
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving fosinopril sodium, hypotension is more likely to occur if the patient has been 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). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. 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. 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 response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

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.

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).

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 following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.
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 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 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.

**Hypersensitivity / Angioedema**

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely 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 not be sufficient.

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 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.

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 4.3 Contraindications).

**Anaphylactoid reactions in Haemodialysis Patients**

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. AN 69) and treated concomitantly 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.

**Desensitisation**
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

**Hepatic failure**
High fosinopril plasma concentrations might occur in patients with impaired hepatic function. 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 who develop jaundice or marked elevations of hepatic enzymes should discontinue fosinopril sodium and receive appropriate medical follow-up.

**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 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. 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.

**Hyperkalaemia**
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, diabetes mellitus or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other medicinal products associated with increases in serum potassium (e.g. heparin). If concomitant use 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).

This medicinal product contains lactose. Patients with rare, hereditary problems of galactose intolerance, the Lapp 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 may occasionally experience an excessive reduction of blood pressure when fosinopril sodium is added. 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).

**Potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other medicinal products associated with increases in serum potassium (e.g. heparin)** (see section 4.4, Hyperkalaemia)

Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. 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.

**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. Use of fosinopril sodium with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4.).

**Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3g/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.

**Other antihypertensive agents**

Combination with other antihypertensive agents such as beta-blockers, methyldopa, 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.
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
Antacids (e.g. aluminium hydroxide, magnesium hydroxide, simeticone) may impair absorption of fosinopril sodium and so the administration of both medicinal products 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 (Kit RIA Digi-Tab® for digoxin). It is recommended to suspend the treatment with fosinopril sodium a few days before performing parathyroid tests.

4.6 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).

**Lactation**

Because no information is available regarding the use of fosinopril sodium during breastfeeding, fosinopril sodium 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. Because of the risk of hypotension occurring as an undesirable effect, which may result in dizziness, it is possible that the product has a negative effect on the ability to drive and use machines.

### 4.8 Undesirable effects

The frequency of adverse reactions listed below is defined using the following convention:

- **Very common** (≥1/10)
- **Common** (≥1/100 to <1/10)
- **Uncommon** (≥1/1,000 to <1/100)
- **Rare** (≥1/10,000 to <1/1,000)
- **Very rare** (<1/10,000)
- **Not known** (cannot be estimated from the available data)

**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

**Psychiatric disorders**

- Uncommon: Depression, confusion

**Nervous system disorders**

- Common: Dizziness, headache
- Uncommon: Cerebral infarction, paraesthesia, somnolence, stroke, syncope, taste disturbances, tremor, sleep disturbance,
- Rare: Dysphasia, memory disturbances, disorientation

**Eye disorders**

- Uncommon: Visual disturbances

**Ear and labyrinth disorders**

- Uncommon: Ear ache, tinnitus, vertigo

**Cardiac disorders**

- Common: Tachycardia
- Uncommon: Angina pectoris, myocardial infarction or cerebrovascular accident, palpitations, cardiac arrest, rhythm disturbances, conduction disturbances
Vascular disorders
Common: Hypotension, orthostatic hypotension
Uncommon: Hypertension, shock, transitory ischaemia
Rare: Flush, haemorrhage, peripheral vascular disease

Respiratory, thoracic and mediastinal disorders
Common: Cough
Uncommon: Dyspnoea, rhinitis, sinusitis, tracheobronchitis
Rare: Bronchospasm, epistaxis, laryngitis/ hoarseness, pneumonia, pulmonary congestion

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea
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
Uncommon: Myalgia
Rare: Arthritis

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

Reproductive and breast disorders
Uncommon: Sexual dysfunction

General disorders and administration site conditions
Common: Chest pain (non-cardiac), weakness
Uncommon: Fever, peripheral oedema, sudden death, thoracic pain
Rare: Weakness in one extremity

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, hyperkalaemia
Rare: Slight increase in haemoglobin, hyponatremia
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.

4.9 Overdose

Limited data are available on overdose among humans.

**Symptoms**
The effects associated with an overdose of ACE inhibitors include hypotension, circulatory shock, electrolyte disturbance, kidney failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and coughing.

**Treatment**
The recommended treatment of overdose is intravenous infusion of normal saline solution. After ingestion of an overdose, the patients should be kept under 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. Measurements to prevent absorption such as gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake to hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered for treatment-resistant bradycardia. Fosinoprilat is poorly removed from the body by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain
ATC code: C09 AA 09

**Mechanism of action**
Fosinopril sodium is the 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.

**Pharmacodynamics**
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.

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 \( C_{\text{max}} \) 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 (\( C_{\text{max}}, \text{AUC} \)) 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.

Metabolism
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 T½ for accumulation of fosinoprilat averaged 11.5 hours. In patients with heart failure, the effective T½ was 14 hours. The elimination of fosinopril is by both hepatic and renal routes.

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 safety data based on conventional studies into general pharmacology, repeated dose
toxicity, gene toxicity and carcinogenic potential do not point to any special risks for humans. Of ACE
inhibitors as a class in itself it has been demonstrated that they cause undesirable effects on the late
fetal development, resulting in fetal death and congenital effects, especially related to the skull.
Fetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported.
These development anomalies are probably results of a direct effect of ACE inhibitors on the fetal
renin-angiotensin system and partially also of ischemia due to hypotension in the mother, diminished
fetal-placental blood flow and reduced oxygen/food supply to the fetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, anhydrous
crospovidone type A (E1202)
zinc stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Aluminium/aluminium blister: 3 years
HDPE bottles: 3 years

6.4 Special precautions for storage

Do not store above 25° C.
Store in the original package in order to protect from moisture.

Bottle: Keep the bottle tightly closed.

6.5 Nature and contents of container

Aluminium/aluminium blister packs of 4, 14, 20, 21, 28, 30, 50, 56, 60, 100 and 400 tablets.
HDPE bottles with PP screw caps and a silica gel desiccant containing 30, 60, 100 and 400 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[to be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[to be completed nationally]
9. **DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

[to be completed nationally]

10. **DATE OF REVISION OF THE TEXT**