SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MONOPRIL 20 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Fosinopril sodium ..... 20 mg

Inactive ingredients:

Anhydrous lactose ..... 126 mg
Sodium stearyl fumarate ..... 3 mg
See Section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablet
White to almost white, round tablets with "DEVA M20" printed on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension: MONOPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with another antihypertensive agent, such as a thiazide diuretic (see Sections 4.3, 4.4, 4.5, and 5.1).

Heart Failure: MONOPRIL is used in combination with a diuretic for the treatment of heart failure (see Sections 4.3, 4.4, 4.5, and 5.1). In these patients, fosinopril alleviates symptoms, improves exercise tolerance, reduces the severity of heart failure, and lowers the rate of hospitalizations due to heart failure.

4.2 Dosage and administration

Dosage/frequency and duration of administration:

Hypertension: Prior to treatment, it is helpful to obtain information regarding the patient's previous antihypertensive medications, blood pressure levels, salt and/or fluid restrictions, and other clinical conditions. If possible, the patient should discontinue their previous antihypertensive medication a few days before starting MONOPRIL.

Unless otherwise advised by the physician, the initial dose of MONOPRIL is 10 mg once daily. Treatment should be adjusted after 4 weeks based on changes in blood pressure. The usual dose is 10–40 mg once daily. If blood pressure is not adequately controlled with MONOPRIL, a diuretic may be added (see Sections 4.3, 4.4, 4.5, and 5.1).

When MONOPRIL is administered to a patient receiving diuretic therapy, treatment should be initiated under medical supervision and the patient should be closely monitored for the first few hours until blood pressure stabilizes. To prevent hypotension, diuretic therapy should be discontinued two or three days before starting MONOPRIL.

Heart Failure: The recommended starting dose of MONOPRIL is 10 mg once daily. The patient should be closely monitored at the start of treatment. If the starting dose of MONOPRIL is well tolerated, the dose may be increased weekly based on clinical response, up to a single daily dose of 40 mg. If the hypotension observed after the initial dose is carefully managed, no dose adjustment is necessary. MONOPRIL should be used in combination with a diuretic (see Sections 4.3, 4.4, 4.5, and 5.1).

Method of administration:
MONOPRIL tablets should be taken with an adequate amount of water (e.g., half a glass).

Additional information for specific populations
Renal/Hepatic impairment:
Since fosinoprilat is eliminated via both pathways, dose adjustment is generally not necessary in patients with renal or hepatic impairment.

Pediatric population:
The safety and efficacy of MONOPRIL in children and adolescents under 18 years of age have not been established.

Geriatric population:
No dose adjustment is required in patients over 65 years of age (see Section 4.4).

4.3 Contraindications

- In patients with a history of allergy to fosinopril sodium or other angiotensin-converting enzyme (ACE) inhibitors, or to the excipients listed in Section 6.1,
- In patients with a history of angioedema,
- Renal artery stenosis (bilateral or unilateral in one kidney),
- Cardiogenic shock,
- During pregnancy,
- The concomitant use of MONOPRIL with aliskiren-containing medications is contraindicated in patients with diabetes mellitus or renal impairment (GFR< 60 mL/min/1.73 m²) (see Sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Warnings
Hypotension:

MONOPRIL has rarely been associated with hypotension in cases of uncomplicated hypertension. As with other ACE inhibitors, the likelihood of symptomatic hypotension is higher in patients receiving intensive diuretic therapy and/or on a salt-restricted diet, or in patients undergoing dialysis. Volume and/or salt depletion should be corrected before initiating fosinopril therapy. A transient hypotensive response to other doses that can be administered without difficulty following salt and/or volume replacement is not a contraindication.

In patients with congestive heart failure, whether related to renal failure or not, ACE inhibitor therapy may cause severe hypotension associated with oliguria or azotemia, and rarely, acute renal failure and death. In such patients, MONOPRIL therapy should be initiated under close medical supervision. Patients should be closely monitored during the first two weeks of treatment and whenever the dose of fosinopril or a diuretic is increased.

In patients with normal or low blood pressure who are receiving intensive diuretic therapy or who are hyponatremic, a reduction in the diuretic dose should be considered.

Hypotension alone is not a reason to discontinue fosinopril therapy. The degree of this decrease is greatest during the early treatment period. This effect stabilizes within one or two weeks and typically returns to pre-treatment levels without a decrease in therapeutic efficacy.

Renal impairment:
In hypertensive patients with renal artery stenosis in one or both kidneys, blood urea nitrogen and serum creatinine may increase during ACE inhibitor therapy. These increases are usually reversible upon discontinuation of treatment. In these patients, renal function should be monitored during the first few weeks of treatment.

In some hypertensive patients without apparent pre-existing renal vascular disease, minor or transient increases in blood urea nitrogen and serum creatinine may occur when fosinopril is administered with a diuretic. This effect is more likely in patients with pre-existing renal disease. A reduction in the MONOPRIL dose may be necessary.

In patients with severe congestive heart failure, where renal function may be dependent 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.

Anaphylactoid reactions during desensitization:
Life-threatening anaphylactoid reactions have been observed in two patients receiving desensitization therapy with hymenoptera venom while concurrently taking enalapril, another ACE inhibitor. In these same patients, these reactions did not occur when ACE inhibitors were temporarily discontinued; however, they reoccurred upon accidental re-exposure to the venom.

Therefore, caution should be exercised when performing such desensitization procedures in patients receiving ACE inhibitor therapy.

Anaphylactoid reactions during contact with high-flux dialysis/lipoprotein apheresis membranes:
Anaphylactoid reactions have been reported in patients undergoing hemodialysis with high-flux dialysis membranes during treatment with ACE inhibitors. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption. In these patients, the use of a different type of dialysis membrane or a different class of medication should be considered.

Angioedema of the head and neck:
Angioedema has been observed in the extremities, face, lips, mucous membranes, tongue, glottis, or larynx in patients receiving ACE inhibitor therapy. If such symptoms occur during treatment with MONOPRIL, therapy should be discontinued.

Very rarely, fatal cases of angioedema associated with laryngeal or tongue edema have been reported. In patients with angioedema involving the tongue, glottis, and larynx, and particularly in those who have undergone airway surgery, airway obstruction may develop. In such cases, adrenaline (epinephrine) should be administered immediately as emergency treatment and/or measures should be taken to ensure the airway remains open. The patient should be kept under close medical observation until symptoms have completely resolved.

Intestinal angioedema:
Intestinal angioedema has been rarely reported in patients treated with ACE inhibitors. In these patients, abdominal pain (with or without nausea and vomiting) has been observed; in some cases, there is no history of facial angioedema, and C-1 esterase levels are normal. The diagnosis of angioedema is made through procedures such as abdominal CT scans or ultrasounds, or during surgery, and symptoms resolve upon discontinuation of the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis for patients taking an ACE inhibitor who present with abdominal pain.

Hepatic impairment:
Very rarely, a syndrome characterized by cholestatic jaundice or hepatitis, progressing to fulminant hepatic necrosis and death (in some cases), has been associated with the use of ACE inhibitors. The mechanism of this syndrome is not understood. In patients who develop jaundice or have a significant elevation in hepatic enzymes during treatment with MONOPRIL, MONOPRIL therapy should be discontinued and appropriate treatment initiated.

Hepatic dysfunction:

Plasma levels of fosinopril may be elevated in patients with hepatic impairment. In a study conducted in patients with alcoholic or biliary cirrhosis, the apparent total body clearance of fosinoprilat was reduced, and plasma AUC levels approximately doubled.

Hyperkalemia:
Elevations in serum potassium levels have been observed in some patients receiving ACE inhibitor therapy, including fosinopril. The risk of hyperkalemia primarily applies to patients with conditions such as renal insufficiency or diabetes mellitus who are also taking potassium-sparing diuretics, potassium supplements, potassium-containing agents, or other medications that may increase serum potassium levels (e.g., heparin).

Neutropenia/Agranulocytosis:
Reversible agranulocytosis and bone marrow depression caused by ACE inhibitors have been rarely reported. Such cases have been observed more frequently in patients with renal failure, particularly those also suffering from collagen vascular diseases such as systemic lupus erythematosus or scleroderma. White blood cell counts should be monitored in these patients.

Surgery/Anesthesia:
ACE inhibitors may potentiate the hypotensive effects of anesthetics and analgesics. If hypotension develops in a patient receiving an ACE inhibitor who is scheduled for surgery or anesthesia, this condition is usually corrected by intravenous fluid administration.

Pediatric population:
Safety and efficacy in children have not been established.

Use in the elderly:
In clinical studies, no significant differences in efficacy or safety were observed between elderly patients (65 years and older) and younger patients receiving fosinopril; however, it should be noted that some elderly patients may be more sensitive.

Precautions
Cough:
Cough has been reported with the use of ACE inhibitors. Typically, the cough is nonproductive and persistent, and resolves upon discontinuation of therapy. Cough induced by an ACE inhibitor should be considered in the differential diagnosis of cough.

Diabetic patients:
During the first month of treatment with ACE inhibitors, glycemic control in patients treated with oral antidiabetic agents or insulin should be closely monitored (see Section 4.5).

Pre-treatment assessment of renal function:
Hypertensive patients should be evaluated for renal function prior to initiating treatment and during treatment (where appropriate).

Aortic stenosis, mitral stenosis, and hypertrophic cardiomyopathy:
In patients with severe forms of these conditions and a constant cardiac output, fosinopril may cause a significant drop in blood pressure because they cannot compensate for the increase in cardiac output with a decrease in peripheral resistance.

Ethnic factors:
The incidence of angioedema caused by ACE inhibitors is higher in Black patients than in non-Black patients. When fosinopril is used alone to treat hypertension, a reduced therapeutic effect may be observed in patients of African-Caribbean descent.

Pregnancy:
ACE inhibitors should not be used during pregnancy. In cases where treatment with ACE inhibitors is not essential, patients planning to become pregnant should switch to an alternative antihypertensive agent with a suitable safety profile for use during pregnancy. Upon confirmation of pregnancy, ACE inhibitors should be discontinued immediately, and alternative therapy should be initiated when appropriate (see Sections 4.3 and 4.6).

Fetal/Neonatal morbidity and mortality:
When used during pregnancy, ACE inhibitors may harm the fetus and may even cause death.

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, syncope, and hyperkalemia, and may lead to impaired renal function (including acute kidney injury). Since the combination of ACE inhibitors, angiotensin II receptor blockers, or aliskiren leads to dual blockade of the RAAS, their concurrent use is not recommended (see Sections 4.5 and 5.1).

If dual blockade therapy is deemed absolutely necessary, it should be administered only under specialist supervision, and renal function, electrolytes, and blood pressure should be closely and frequently monitored. ACE inhibitors and angiotensin II receptor blockers should not be used together in patients with diabetic nephropathy.

Lactose: Contains lactose. Patients with rare hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not use this medication.

Sodium: This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet; therefore, it is essentially “sodium-free.”

4.5 Interactions with other medicinal products and other forms of interaction

Antacids:

Antacids (e.g., aluminum hydroxide, magnesium hydroxide, and simethicone) may impair the absorption of MONOPRIL. Therefore, MONOPRIL and antacids should be administered at least 2 hours apart.

Nonsteroidal anti-inflammatory drugs (NSAIDs): The use of nonsteroidal anti-inflammatory drugs and aspirin in doses exceeding 3 g per day may impair the antihypertensive effect of ACE inhibitors. However, the concomitant use of fosinopril and NSAIDs (including aspirin) is not associated with an increase in clinically significant adverse reactions. As with other ACE inhibitors, the concurrent use of fosinopril and NSAIDs in some patients with renal insufficiency may lead to further deterioration of renal function.

Lithium:

Increased serum lithium levels and an increased risk of lithium toxicity have been reported in patients taking ACE inhibitors concomitantly with lithium. Caution should be exercised when MONOPRIL is used with lithium, 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, particularly in cases of low-renin hypertension. Other nonsteroidal anti-inflammatory drugs (e.g., aspirin) may have similar effects.

Diuretics:

In patients taking diuretics—especially those who have recently started diuretic therapy—as well as in patients on strict salt restriction or undergoing dialysis, a rapid drop in blood pressure may rarely occur within the first hour following administration of the initial dose of MONOPRIL.

Other antihypertensive agents:

The combined use of other antihypertensive agents, such as beta-blockers, methyldopa, calcium channel blockers, and diuretics, may enhance the antihypertensive effect.

Immunosuppressants:

Concomitant use of fosinopril with immunosuppressants (e.g., azathioprine) may increase the risk of leukopenia.

Combinations not recommended:

Potassium supplements and potassium-sparing diuretics:
Fosinopril may mitigate the potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (e.g., spironolactone, amiloride, and triamterene) or potassium supplements may increase the risk of hyperkalemia. Therefore, if the concomitant use of MONOPRIL and such agents is indicated, they should be administered with caution, and the patient's serum potassium levels should be monitored frequently.

Clinical trial data indicate that dual blockade of the renin-angiotensin-aldosterone system (RAAS), the combined use of ACE inhibitors, angiotensin II receptor blockers, or aliskiren to achieve dual blockade is associated with a higher incidence of adverse events such as hypotension, hyperkalemia, and impaired renal function (including acute kidney injury) compared to the use of a single RAAS-active agent (see Sections 4.3, 4.4, and 5.1).

Other medications:
Antidiabetics:
Epidemiological studies have shown that the concomitant use of ACE inhibitors with antidiabetic medicinal products (insulin, oral hypoglycemic agents) may increase the risk of hypoglycemia and enhance the blood glucose-lowering effect. This event is more likely to occur in patients with renal impairment and during the first weeks of combination therapy.
In pharmacokinetic studies conducted with nifedipine, propranolol, cimetidine, metoclopramide, and propantheline, the bioavailability of fosinoprilat remains unchanged when co-administered with any of these medications.

Fosinopril has been used concomitantly with paracetamol, antihistamines, lipid-lowering agents, or estrogen without causing clinically significant adverse effects.

Interactions with serological tests:
MONOPRIL may cause serum digoxin levels measured using the activated charcoal absorption method to appear falsely low. In such cases, other kits based on the antibody-coated tube method may be used. MONOPRIL treatment should be discontinued a few days prior to parathyroid function tests.

4.6 Pregnancy and lactation
General Recommendation
Pregnancy Category: D.

Women of childbearing potential/Contraception
Appropriate contraception should be used in women of childbearing potential, and an appropriate alternative treatment should be initiated prior to a planned pregnancy.

Pregnancy

The use of ACE inhibitors during the first trimester of pregnancy is not recommended (see Section 4.4). The use of ACE inhibitors during the second and third trimesters is contraindicated (see Sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following the use of ACE inhibitors during the first trimester of pregnancy is inconclusive. However, a small increase in this risk cannot be ruled out. In cases where treatment with ACE inhibitors is not essential, treatment for patients planning to become pregnant should be switched to an alternative antihypertensive agent with a suitable safety profile throughout the pregnancy. Upon confirmation of pregnancy, ACE inhibitors should be discontinued immediately, and alternative therapy should be initiated when appropriate.

It is known that exposure to ACE inhibitors during the second and third trimesters causes fetotoxicity (decreased renal function, oligohydramnios, delayed ossification of the skull) and neonatal toxicity (renal failure, hypotension, hyperkalemia) in humans (see Section 5.3). If exposure to an ACE inhibitor occurs during the second trimester, monitoring of renal function and the skull via ultrasound is recommended. Infants of mothers using ACE inhibitors should be closely monitored for hypotension (see Sections 4.3 and 4.4).

Lactation
There is limited data on the use of fosinopril during lactation. The use of fosinopril during lactation is not recommended, and alternative treatments with a higher safety profile should be preferred (especially when breastfeeding a newborn or premature infant).

Reproductive capacity / Fertility
The effect on fertility is unknown.

4.7 Effects on the ability to drive and use machines
Although MONOPRIL is not expected to affect the ability to drive or use machines, it may cause side effects such as dizziness, vertigo, or hypotension. Patients should ensure they have not experienced such effects before driving or using machines.

4.8 Adverse Effects
Adverse effects observed in patients treated with MONOPRIL are generally mild and transient.

The following frequency categories have been used:
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 available data)

Infections and infestations

Common:	Upper respiratory tract infection, pharyngitis, rhinitis, viral infections
Not known:	Pneumonia, laryngitis, sinusitis, tracheobronchitis

Diseases of the blood and lymphatic system

Not known:	Eosinophilia, leukopenia, lymphadenopathy, neutropenia

Metabolic and nutritional disorders

Not known:	Loss of appetite, appetite disorder, weight change, gout, hyperkalemia

Psychiatric disorders

Common:	Mood changes, sleep disorders
Not known:	Depression, abnormal behavior, confusion

Nervous system disorders

Common:	Dizziness, headache, paresthesia
Uncommon:	Syncope
Not known:	Cerebral infarction, transient ischemic attack, tremor, balance disorder, memory impairment, somnolence, cerebrovascular event

Eye disorders

Common:	Eye disorders, visual disturbances

Ear and inner ear disorders:

Not known:	Ear pain, tinnitus, vertigo

Cardiac diseases

Common:	Arrhythmia, palpitations, angina pectoris
Not known:	Tachycardia, cardiopulmonary arrest, myocardial infarction, cardiac arrest, cardiac conduction disorders

Vascular diseases

Common:	Hypotension, orthostatic hypotension
Uncommon:	Shock
Not known:	Flushing, hypertensive crisis, hemorrhage, peripheral vascular disease, hypertension

Respiratory, chest disorders, and mediastinal diseases

Common:	Cough, sinus disorders

Not known: Dyspnea, bronchospasm, pulmonary congestion, dysphonia, nosebleeds, sinusitis, pleuritic chest pain

Gastrointestinal diseases
Common: Nausea, vomiting, diarrhea, abdominal pain, dyspepsia, dysgeusia
Not known: Pancreatitis, swelling of the tongue, difficulty swallowing, constipation, dry mouth, gas, oral problems, abdominal distension

Hepatobiliary disorders
Not known: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Angioedema
Not known: Hyperhidrosis, ecchymosis, pruritus, dermatitis, urticaria

Musculoskeletal disorders, connective tissue and bone diseases
Common: Musculoskeletal pain, muscle pain
Not known: Muscle weakness, arthritis

Kidney and urinary tract diseases
Common: Abnormalities in urination
Not known: Kidney failure

Reproductive system and breast diseases
Common: Sexual dysfunction
Not known: Prostate disease

General disorders and conditions related to the affected area
Common: Fatigue, chest pain, edema, asthenia
Not known: Peripheral edema, pain, fever

Investigations
Not known: Weight gain, changes in liver function tests

In clinical trials with fosinopril, the incidence of adverse effects in elderly patients (65 years and older) is no different from that in younger patients.

Hypotension or syncope is a reason for discontinuing treatment in 0.3% of patients.

A combination of cough, bronchospasm, and eosinophilia was observed in two patients treated with fosinopril.

Safety data regarding the use of fosinopril in the pediatric population are limited, and only short-term exposure has been evaluated. In a randomized clinical trial involving 253 children and adolescents aged 6 to 16 years, the following adverse events occurred during the 4-week double-blind phase: headache (13.9%), hypotension (4.8%), cough (3.6%), hyperkalemia (3.6%), elevated serum creatinine levels (9.2%), and elevated serum creatine kinase levels (2.9%). Unlike in adults, CK levels were elevated in this study (without transient or clinical symptoms). The long-term effects of fosinopril on growth, puberty, and overall development have not been studied.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose
Symptoms
Symptoms of overdose may include severe hypotension, electrolyte imbalance, and renal failure. The patient must be closely monitored following an overdose. Therapeutic measures depend on the type and severity of symptoms. Methods to prevent absorption and accelerate elimination should be employed. If severe hypotension develops, the patient should be placed in the shock position and normal saline solution should be administered intravenously rapidly. Treatment with angiotensin II (if possible) should be considered. The use of high-flux polyacrylonitrile dialysis membranes should be avoided. Serum electrolytes and creatinine should be monitored frequently.

Treatment:
A: Activated charcoal: Administered as a suspension (240 mL water/30 g charcoal). Standard dose: 25 to 100 g for adults and adolescents; 25 to 50 g for children; and 1 g/kg for infants under 1 year of age
B: Hypotension: 10 to 20 mL/kg of isotonic solution is administered by infusion; the patient is placed in the Trendelenburg position. If hypotension persists, dopamine (5 to 20 micrograms/kg/min) or norepinephrine (0.1 to 0.2 micrograms/kg/min) is administered; the dose is adjusted according to the desired effect.

1. In patients who do not respond to volume and pressor agents, angiotensin infusion administered at a dose range of 8.5 to 18 micrograms/min has been successful in reversing hypotension.

2. Naloxone has also been effective in some hypotensive patients.

C: Angioedema: Antihistamines and corticosteroids are administered. The airway is secured, and oxygen is administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-Converting Enzyme Inhibitors
ATC Code: C09AA09

Mechanism of action:
Fosinopril is the prodrug of fosinoprilat, a long-acting, active ACE inhibitor (in ester form). When administered orally, fosinopril is rapidly and completely metabolized to its active form, fosinoprilat. By specifically binding to the active site of the angiotensin-converting enzyme via its phosphinate group, it inhibits the conversion of angiotensin I to the vasoconstrictor angiotensin II. The reduction in angiotensin II decreases vasopressor activity and aldosterone secretion. This latter effect may cause a slight increase in serum potassium, along with sodium and fluid loss.

ACE inhibition also prevents the breakdown of bradykinin, a potent vasodilator peptide with antihypertensive effects. Fosinopril is effective even in hypertensive patients with low renin levels.

In patients with heart failure, the benefits of fosinopril are thought to arise primarily from the suppression of the renin-angiotensin-aldosterone system; inhibition of angiotensin-converting enzyme leads to reductions in both preload and afterload.

The antihypertensive effect begins 1 hour after a single dose. Maximum effect is observed 3–6 hours later. The antihypertensive effect persists for 24 hours with the normal daily dose.

Pharmacodynamic effects:
Blood pressure decreases both while standing and in the supine position. Orthostatic effects and tachycardia are rare but may occur in patients with salt and volume depletion. The decrease in blood pressure may be progressive, and several weeks may be required to achieve the therapeutic effect.

The blood pressure-lowering effects of fosinopril and thiazide-type diuretics are additive.

In heart failure, fosinopril improves symptoms and exercise tolerance, reduces the severity of heart failure, and decreases the frequency of hospitalizations due to heart failure.

Two large randomized 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 combined use of an ACE inhibitor with an angiotensin II receptor blocker.

The ONTARGET trial was conducted in patients with type 2 diabetes mellitus who had a history of cardiovascular or cerebrovascular disease or who had type 2 diabetes mellitus with established end-organ damage. The VA NEPHRON-D trial was conducted in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies did not demonstrate a significant benefit regarding renal and/or cardiovascular outcomes and mortality; compared to monotherapy, an increased risk of hyperkalemia, acute kidney injury, and/or hypotension was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and angiotensin II receptor blockers.

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

The ALTITUDE (Aliskiren Trial in Type 2 Diabetes using Cardiovascular and Renal Disease Endpoints) study was designed to evaluate the benefit of adding aliskiren to standard treatment with an ACE inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus who had chronic kidney disease, cardiovascular disease, or both. The study was terminated early due to an increased risk of adverse outcomes. In the aliskiren group, both cardiovascular deaths and strokes occurred numerically more frequently compared to the placebo group, and related adverse events and serious adverse events (hyperkalemia, hypotension, and renal dysfunction) were reported more frequently in the aliskiren group than in the placebo group.

Pediatric population

In a randomized, double-blind study involving 252 children and adolescents aged 6 to 16 years with hypertension or high-normal blood pressure, the reduction in blood pressure was evaluated with low (0.1 mg/kg), medium (0.3 mg/kg), and high (0.6 mg/kg) doses of fosinopril administered once daily. At the end of the 4-week treatment period, the mean reduction in systolic blood pressure compared to baseline was similar in children treated with low, moderate, and high doses of fosinopril. No dose-response relationship was established among the three doses. The optimal dosage in children has not been determined. There is no established appropriate dose for children weighing less than 50 kg.

5.2 Pharmacokinetic Properties

General characteristics

Absorption:

MONOPRIL is absorbed at an average rate of 30–40% following oral administration. The absorption of fosinopril is not affected by food in the gastrointestinal tract; however, the rate of absorption may be slowed. Maximum plasma concentration is reached approximately 3 hours after administration and is independent of the dose administered.

Distribution:
Fosinoprilat binds extensively to serum proteins (≥ 95%), but its binding to cellular components of the blood is negligible.

Elimination:
Following intravenous administration, fosinopril is eliminated via the liver and kidneys. In hypertensive patients with normal renal and hepatic function receiving repeated doses of fosinopril, the elimination half-life of fosinoprilat is 11.5 hours; in patients with heart failure, it is 14 hours.

Linearity/Non-linearity:
Following a single or multiple oral doses, pharmacokinetic parameters (e.g., C_{max}, AUC) are directly proportional to the administered dose.

Patient Characteristics
Renal impairment:
In patients with renal insufficiency (creatinine clearance < 80 mL/min/1.73 m²), the total body clearance of fosinoprilat is approximately half that of patients with normal renal function; however, there are no significant changes in absorption, bioavailability, or protein binding. Fosinoprilat clearance does not show a significant difference depending on the degree of renal insufficiency; reduced renal elimination is balanced by increased hepatobiliary elimination. A slight increase in plasma AUC levels (less than twice the normal level) has been observed in patients with various degrees of renal impairment, including end-stage renal failure (creatinine clearance < 10 mL/min/1.73 m²).

Hepatic impairment:
In patients with hepatic insufficiency (alcoholic or biliary cirrhosis), the hydrolysis of fosinopril is not significantly reduced, but the hydrolysis rate may be slowed. In patients with hepatic insufficiency, the apparent total body clearance of fosinoprilat is approximately half that of individuals with normal hepatic function.

Pediatric population
Limited data are available regarding children and adolescents from a single-dose pharmacokinetic study conducted in 19 hypertensive patients aged 6–16 years who received a 0.3 mg/kg fosinopril solution.

It should be determined whether the AUC and C_{max} values of fosinoprilat (the active form of fosinopril) in children aged 6–16 years are comparable to those observed in adults receiving 20 mg of fosinopril as a solution.

The terminal elimination half-life of fosinoprilat was 11–13 hours and was similar across all phases of the study.

5.3 Preclinical safety data
Animal studies indicate a toxicity profile consistent with the pharmacological effects of fosinopril. No evidence of carcinogenicity was observed in studies conducted in rodents, and no mutagenic potential was observed in *in vitro* or *in vivo* studies.

6. PHARMACEUTICAL PROPERTIES
6.1 List of excipients
Anhydrous lactose
Povidone K30
Crospovidone
Microcrystalline cellulose
Sodium stearyl fumarate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at room temperature below 25°C in its original packaging.

It should be stored in a dry place to protect it from moisture.

6.5 Nature and contents of container
Available in blister packs containing 28 tablets.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Deva Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
34303 No:1 Küçükçekmece/Istanbul/TÜRKİYE

Tel: 0212 692 92 92
Fax: 0212 697 00 24
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8. MARKETING AUTHORISATION NUMBER(S)

226/31

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization : 06.10.2010
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT