SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MONOPRIL PLUS 10 mg/12.5 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active ingredient:

Fosinopril sodium ..... 10 mg
Hydrochlorothiazide (HCTZ) ..... 12.5 mg

Inactive ingredients:

Anhydrous lactose (derived from cow's milk) ..... 80.3 mg
Lactose monohydrate (derived from cow's milk) ..... 83 mg

See Section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Tablet
Round, biconvex, peach-colored tablets with "DEVA MP 10" printed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MONOPRIL PLUS is indicated for the treatment of hypertension (see Sections 4.3, 4.4, 4.5, and 5.1).

4.2 Dosage and Administration

Dosage/frequency and duration of administration:

Doses should be adjusted individually.

Adults and the elderly:
The usual dose is 10/12.5 mg or 20/12.5 mg MONOPRIL PLUS tablets once daily (see Sections 4.3, 4.4, 4.5, and 5.1).

Method of administration:

MONOPRIL PLUS is taken in the morning with an adequate amount of water (e.g., a glass).

Additional information for specific populations

Renal/Hepatic impairment:

In patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min/1.73 m², serum creatinine approximately ≤ 3 mg/dL or 265 µmol/L), the usual daily dose is recommended. However, in patients with severe renal impairment (creatinine clearance < 30

mL/min/1.73 m², serum creatinine approximately > 3 mg/dL or 265 µmol/L), loop diuretics are preferred over thiazides (see Section 4.4).
In patients with impaired liver function, no adjustment of the initial dose of MONOPRIL PLUS is necessary.

Rarely, cholestatic jaundice, hepatic necrosis, and occasionally death related to these conditions may occur following the administration of ACE inhibitors. The mechanism of this syndrome has not yet been elucidated. Patients who develop jaundice or elevated liver enzymes while starting MONOPRIL PLUS therapy should discontinue MONOPRIL PLUS (fosinopril sodium and hydrochlorothiazide) and be placed under medical observation.

MONOPRIL PLUS should be used with caution in individuals with impaired liver function or progressive liver disease, as even minor changes in fluid and electrolyte balance may lead to hepatic coma. Additionally, since the metabolism of fosinopril to fosinoprilat is normally dependent on hepatic esterases, plasma levels of fosinopril may increase in patients with impaired liver function. In a study involving patients with alcoholic or biliary cirrhosis, the rate of fosinoprilat hydrolysis (not the rate itself) was reduced. In these patients, fosinoprilat clearance was also reduced, and the area under the fosinoprilat-time curve increased approximately twofold.

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

Geriatric population:
Based on clinical experience, no dose adjustment is considered necessary in patients aged 65 and older with normal renal and hepatic function (see Section 4.4).

4.3 Contraindications

MONOPRIL PLUS should not be used in the following situations:
- It is contraindicated in patients with an allergy to fosinopril sodium or other angiotensin-converting enzyme (ACE) inhibitors, other thiazides such as hydrochlorothiazide or sulfonamides (caution should be exercised regarding possible cross-reactions), or any of the other components listed in Section 6.1. Hypersensitivity reactions are more likely to occur in patients with a known history of allergies or bronchial asthma.
- In cases where angioedema has occurred due to prior treatment with an ACE inhibitor,
- In cases of hereditary or idiopathic angioedema,
- In severe renal impairment (creatinine clearance < 30 mL/min),
- In severe liver dysfunction (hepatic precoma/coma),
- Cardiogenic shock,
- Renal artery stenosis,
- In cases of anuria,

- It is contraindicated during pregnancy.
- The concomitant use of MONOPRIL PLUS with aliskiren-containing medications is contraindicated in patients with diabetes mellitus or renal insufficiency (GFR < 60 mL/min/1.73 m²) (see Sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan. Fosinopril should 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

Angioedema of the head and neck

Angioedema has been observed in patients treated with ACE inhibitors (including fosinopril sodium). If angioedema involves the tongue, glottis, and larynx, airway obstruction may develop and be fatal. Emergency treatment must be initiated immediately. Edema limited to the face, oral mucosa, lips, and extremities has mostly resolved after discontinuation of fosinopril, with medical treatment required only in some cases. Even in cases where only tongue edema is present without respiratory failure, treatment with antihistamines and corticosteroids is not always sufficient, so the patient may require prolonged observation.

Very rarely, fatal cases of angioedema associated with laryngeal or tongue edema have been reported. In cases involving the tongue, glottis, and larynx, airway obstruction is possible, particularly in patients with a history of airway surgery. In such cases, emergency treatment must be initiated immediately; depending on the situation, administration of epinephrine and/or maintenance of airway patency may be necessary. The patient must remain under frequent medical supervision until symptoms have completely and permanently resolved.

ACE inhibitors cause angioedema more frequently in Black patients than in White patients.

In patients with a known history of angioedema unrelated to an ACE inhibitor, the risk of angioedema occurring during treatment with an ACE inhibitor is higher (see Section 4.3).

Hypersensitivity/Angioedema

The use of ACE inhibitors in combination with sacubitril/valsartan is contraindicated due to an increased risk of angioedema. Treatment with sacubitril/valsartan should not be initiated until at least 36 hours after the last dose of fosinopril. Treatment with fosinopril should not be initiated within 36 hours of the last dose of sacubitril/valsartan (see Sections 4.3 and 4.5).

The use of ACE inhibitors in combination with rasecadotril, mTOR inhibitors (e.g., sirolimus, everolimus, temsirolimus), and vildagliptin may increase the risk of angioedema (e.g., swelling of the airways or tongue, with or without respiratory distress) (see Section 4.5). Caution should be exercised when initiating rasecadotril, mTOR inhibitors (e.g., sirolimus, everolimus, temsirolimus), and vildagliptin in a patient currently taking an ACE inhibitor.

Anaphylactoid reactions in hemodialysis patients

Anaphylactoid reactions have been reported in patients undergoing dialysis with high-flux membranes (e.g., AN 69) and being treated with an ACE inhibitor. In these patients, consideration should be given to using a different type of dialysis membrane or an antihypertensive agent from a different class.

Anaphylactoid reactions during low-density lipoprotein (LDL) apheresis

Rarely, life-threatening anaphylactoid reactions have occurred in patients receiving ACE inhibitors during LDL apheresis with dextran sulfate. These reactions were prevented by temporarily discontinuing ACE inhibitor therapy prior to each apheresis.

Intestinal angioedema

Intestinal angioedema has been rarely reported in patients treated with ACE inhibitors. These patients have experienced abdominal pain (with or without nausea and vomiting); in some cases, facial edema had previously occurred, and C-1 esterase levels were normal. The diagnosis of angioedema is made through procedures involving abdominal CT scans or ultrasound, or during surgery, and symptoms resolve upon discontinuation of the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis for patients taking ACE inhibitors who present with abdominal pain.

Anaphylactoid reactions during desensitization

Life-threatening anaphylactoid reactions have been observed in two patients receiving desensitization therapy with hymenoptera venom while also 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.

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia, and anemia have been observed during treatment with ADE inhibitors. Neutropenia occurs rarely in patients with normal renal function and no other complicating factors. Agranulocytosis and bone marrow depression have frequently been observed in patients with impaired renal function, particularly those with concomitant collagen vascular diseases such as systemic lupus erythematosus or scleroderma. Neutropenia and agranulocytosis resolve after discontinuation of the ACE inhibitor. Fosinopril must be used with extreme caution in patients receiving collagenous, immunosuppressive therapy, allopurinol, or procainamide, or a combination of these risk factors, especially if there is evidence of impaired renal function. In some such patients, severe infections unresponsive to intensive antibiotic therapy have developed in certain cases. If fosinopril is used in the presence of the specified risk factors, regular monitoring of white blood cell counts is recommended; patients should be instructed to report any symptoms that may indicate an infection to their physician. Rarely, agranulocytosis and bone marrow depression have also been reported with thiazide therapy.

Hypotension

MONOPRIL PLUS has rarely been associated with hypotension in cases of uncomplicated hypertension. Symptomatic hypotension occurs more frequently in patients treated with fosinopril who have salt and/or volume depletion due to long-term diuretic therapy (resulting from dietary salt restriction, dialysis, diarrhea, or vomiting) or in cases of severe renin-dependent hypotension (see Sections 4.5 and 4.8). Volume and/or salt depletion must be corrected before initiating MONOPRIL PLUS therapy. Patients at high risk of symptomatic hypotension should be closely monitored frequently at the start of treatment and during dose adjustments. This applies to patients with cardiac or cerebrovascular ischemia, in whom a marked drop in blood pressure could lead to myocardial infarction or stroke.

In patients with congestive heart failure, whether related to renal insufficiency or not, ACE inhibitor therapy may cause severe hypotension associated with oliguria or azotemia, and rarely, acute renal failure and death. In such patients, treatment with MONOPRIL PLUS 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 the diuretic is increased.

Thiazides potentiate the effects of other antihypertensive agents. Following sympathectomy, diuretics containing thiazides may also exhibit a more pronounced blood pressure-lowering effect.

If hypotension occurs, the patient should be placed in a supine position, and if necessary, normal saline (0.9% NaCl) should be administered via intravenous infusion. A transient hypotensive response to subsequent doses that can be safely administered after salt and/or volume replacement is not a contraindication.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the combined 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 it leads to dual blockade of the RAAS, the combined use of ACE inhibitors, angiotensin II receptor blockers, or aliskiren 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.

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 can harm the fetus and may even cause death.

Hepatic impairment
Plasma levels of fosinopril may increase in patients with impaired hepatic function. 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 PLUS, MONOPRIL PLUS therapy should be discontinued and appropriate treatment initiated.

Hepatic dysfunction
MONOPRIL PLUS should be used with caution in patients with impaired hepatic function or progressive liver disease, as even minor changes in fluid and electrolyte balance may lead to hepatic coma (see Section 4.3). Plasma levels of fosinopril/hydrochlorothiazide may be elevated in patients with impaired liver function. In a study involving patients with alcoholic or biliary cirrhosis, the apparent total body clearance of fosinoprilat was reduced, and the plasma AUC (area under the curve) approximately doubled.

Renal impairment
No adjustment of the initial dose of fosinopril sodium is required in patients with renal impairment. Routine monitoring of potassium and creatinine is part of standard care for these patients (see Sections 4.2 and 4.3). However, MONOPRIL PLUS should be used with caution in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m²). Cumulative effects of hydrochlorothiazide and hydrochlorothiazide-induced azotemia may occur in patients with renal insufficiency. In susceptible patients, changes in renal function may also occur as a result of inhibition of the renin-angiotensin-aldosterone system by fosinopril.

In patients with heart failure, initiation of treatment with ACE inhibitors may cause not only a decrease in blood pressure but also a deterioration in renal function. In such cases, reversible acute renal failure has been observed in most instances.

In patients with renal artery stenosis in one or both kidneys, increases in blood urea nitrogen and serum creatinine may be observed during ACE inhibitor therapy. These increases are generally reversible upon discontinuation of treatment. This is particularly observed in patients with renal insufficiency. Additionally, in the presence of renovascular hypertension, there is a greater risk of a significant drop in blood pressure and renal failure. In these patients, treatment should be initiated under close medical supervision at short intervals. Since diuretic therapy

may contribute to these complications, diuretic use should be discontinued, and renal function should be monitored during the first weeks of fosinopril sodium therapy.
In some hypertensive patients without pre-existing significant renal vascular disease, mild or transient elevations in blood urea nitrogen and serum creatinine have generally been observed when fosinopril is administered concomitantly with a diuretic. This situation occurs particularly in patients with pre-existing renal insufficiency. It may be necessary to reduce the MONOPRIL PLUS dose and/or discontinue the use of the diuretic and/or the ACE inhibitor.

Electrolyte Imbalance
Serum electrolytes should be monitored at regular intervals in all patients receiving diuretic therapy, as thiazides, including HCTZ, may cause fluid or electrolyte imbalances (hypokalemia, hyponatremia, and hypchloremic alkalosis). Symptoms such as dry mouth, thirst, weakness, lethargy, dizziness, fatigue, muscle pain or cramps, muscle weakness, hypotension, oliguria, tachycardia, or gastrointestinal disturbances such as nausea/vomiting may indicate fluid or electrolyte imbalance, and patients should be monitored regularly. Although hypokalemia may occur, particularly with the use of thiazide diuretics in the presence of diuresis or severe cirrhosis, concomitant administration of fosinopril reduces the risk of diuretic-induced hypokalemia. The risk of hypokalemia is particularly high in patients with liver cirrhosis, in cases of severe diuresis, with inadequate or oral intake of electrolytes, and during concomitant corticosteroid or adrenocorticotropic hormone (ACTH) therapy (see Section 4.5). Dilutional hyponatremia may occur in edematous patients. The net effect of MONOPRIL PLUS may be to increase, decrease, or maintain serum potassium levels.

Observed chloride deficiencies are generally mild and do not require treatment. Thiazides may reduce calcium excretion by the kidneys and may cause a temporary, mild increase in calcium levels without affecting calcium metabolism. In a small number of patients receiving long-term thiazide therapy, hypercalcemia and hypophosphatemia have been observed alongside pathological changes in the parathyroid glands. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulcers) have not been observed. Thiazides should be discontinued prior to performing parathyroid function tests.

Thiazides may increase urinary excretion of magnesium and cause hypomagnesemia.

Metabolic disorders
Hyperuricemia may develop in some patients receiving thiazide therapy, and acute gout attacks may occur. In diabetic patients, insulin requirements may change, and latent diabetes mellitus may flare up during thiazide therapy. Increases in cholesterol and triglyceride levels have also been observed with treatment using thiazide-containing diuretics.

Cough
Cough has been reported with the use of ACE inhibitors, including fosinopril. Characteristically, the cough is nonproductive and persistent, and resolves upon discontinuation

of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia
In patients undergoing surgery or under anesthesia with antihypertensive agents, fosinopril may block the formation of angiotensin II resulting from compensatory renin release. Hypotension resulting from this mechanism can be corrected by volume expansion.

Systemic lupus erythematosus
It has been reported that thiazide diuretics may cause a flare-up or exacerbation of systemic lupus erythematosus.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy
Like other ACE inhibitors, fosinopril sodium should be used with caution in patients with mitral valve stenosis and obstruction of the left ventricular outflow tract (e.g., due to aortic stenosis or hypertrophic cardiomyopathy).

Use in children
Safety and efficacy in children have not been established.

Use in the elderly
In clinical trials, 20% of patients receiving fosinopril/HCTZ were aged 65–75. No general difference in efficacy or safety was observed between these patients and younger patients; however, it should be noted that the elderly may be more sensitive.

Use following kidney transplantation
Since there is no experience with patients who have recently undergone kidney transplantation, the use of fosinopril is not recommended in this patient group.

Ethnic factors:
As with other ACE inhibitors, the blood pressure-lowering effect of fosinopril sodium is weaker in Black patients compared to other population groups; this is likely due to the fact that Black patients with high blood pressure have lower renin levels.

Hyperkalemia:
ACE inhibitors may cause hyperkalemia because they inhibit aldosterone secretion. In patients with normal renal function, this effect is generally not significant. However, hyperkalemia may occur in patients with impaired renal function and/or those receiving potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim, or co-trimoxazole (also known as trimethoprim/sulfamethoxazole), and particularly in patients taking aldosterone antagonists or angiotensin receptor blockers. Potassium-sparing diuretics and angiotensin

receptor blockers should be used with caution in patients taking ACE inhibitors, and serum potassium and renal function should be monitored (see Section 4.5).

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

Hydrochlorothiazide
Endocrine and metabolic effects
Glucose tolerance may be reduced during thiazide therapy. In diabetic patients, adjustment of the dose of insulin or oral antidiabetics may be necessary (see Section 4.5). Latent diabetes mellitus may become apparent during thiazide therapy.

Elevations in cholesterol and triglyceride levels have been observed during thiazide therapy. Thiazide therapy may induce hyperuricemia or trigger gout attacks in certain patients.

Non-melanoma skin cancer
In two epidemiological studies based on the Danish National Cancer Registry, an increase in the risk of non-melanoma skin cancer [basal cell carcinoma and squamous cell carcinoma] was observed with increasing cumulative hydrochlorothiazide exposure. The photosensitizing effect of hydrochlorothiazide may play a role as a potential mechanism in non-melanoma skin cancer.

Patients taking hydrochlorothiazide should be informed about the risk of non-melanoma skin cancer and advised to regularly check their skin for new lesions and report any suspicious skin lesions immediately. Patients should be advised to limit their exposure to sunlight and UV radiation to minimize the risk of skin cancer and to apply adequate protection when exposed. Suspicious skin lesions should be evaluated urgently, including histological biopsy examinations. In patients with a history of non-melanoma skin cancer, the use of hydrochlorothiazide may also require careful re-evaluation. (See also Section 4.8).

Choroidal effusion, acute myopia, and secondary angle-closure glaucoma
Sulfonamides or sulfonamide-derived drugs may cause a specific reaction resulting in choroidal effusion, visual field defects, transient myopia, and acute angle-closure glaucoma. Symptoms include a decrease in visual acuity or an acute onset of ocular pain, typically appearing within hours to weeks after starting the medication. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the medication as quickly as possible. If intraocular pressure cannot be controlled, emergency medical or surgical interventions may be necessary. Risk factors for the development of acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Acute Respiratory Toxicity

Very rare cases of severe acute respiratory toxicity, including acute respiratory distress syndrome (ARDS), have been reported following hydrochlorothiazide administration. The development of pulmonary edema typically occurs within minutes or hours after hydrochlorothiazide administration. Initial symptoms include dyspnea, fever, worsening pulmonary status, and hypotension. If ARDS is suspected, MONOPRIL PLUS therapy should be discontinued and appropriate treatment administered. Hydrochlorothiazide should not be administered to patients who have previously experienced ARDS following hydrochlorothiazide administration.

Other Warnings
Hypersensitivity reactions may occur in patients with or without a history of allergies or bronchial asthma.

Fosinopril sodium/hydrochlorothiazide
Risk of hypokalemia
A combination of an ACE inhibitor and a thiazide diuretic does not eliminate the possibility of hypokalemia. Regular monitoring of potassium levels is required.

Doping test:
Hydrochlorothiazide, which is present in this medication, may cause a positive result in a doping test.

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

4.5 Interactions with other medicinal products and other forms of interaction

Fosinopril sodium
Diuretics
If a diuretic is administered in addition to fosinopril therapy, the blood pressure-lowering effect is generally enhanced.

In patients already taking diuretics, particularly those who have recently started diuretic therapy, the addition of fosinopril sodium may occasionally cause a severe drop in blood pressure. The likelihood of symptomatic hypotension during fosinopril sodium therapy can be reduced by discontinuing diuretic use prior to initiating fosinopril sodium therapy (see Sections 4.2 and 4.4).

Potassium-sparing diuretics, potassium supplements, or potassium-containing salt substitutes
Although serum potassium levels generally remain within normal limits, hyperkalemia may occur in some patients treated with fosinopril. Potassium-sparing diuretics (e.g., spironolactone,

triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may cause significant increases in serum potassium. Caution is also advised when fosinopril is administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic, similar to amiloride. Therefore, the combination of fosinopril with the aforementioned medications is not recommended. If concomitant use is indicated, it should be used with caution, and serum potassium levels should be monitored frequently.

Cyclosporine
Hyperkalemia may occur during the concomitant use of ACE inhibitors with cyclosporine. Monitoring of serum potassium is recommended.

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

Drugs that increase the risk of angioedema
The use of ACE inhibitors in combination with sacubitril/valsartan is contraindicated because it increases the risk of angioedema (see Sections 4.3 and 4.4).
The use of ACE inhibitors in combination with rasecadotril, mTOR inhibitors (e.g., sirolimus, everolimus, temsirolimus), and vildagliptin may increase the risk of angioedema (see Section 4.4).

Lithium
Increases in serum lithium levels and a risk of lithium toxicity have been reported in patients receiving ACE inhibitors concomitantly with lithium. MONOPRIL PLUS and lithium should be used with caution, and frequent monitoring of serum lithium levels is recommended.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid ≥ 3 g/day
Chronic NSAID use may reduce the blood pressure-lowering effect of the ACE inhibitor. NSAIDs and ACE inhibitors have an additive effect on serum potassium levels and may cause a decrease in renal function. This effect is generally reversible. In rare cases, particularly in elderly patients with impaired renal function or in dehydrated patients, renal failure may occur.

Other antihypertensive medications
Combination with other antihypertensive agents, such as beta-blockers, methyldopa, calcium channel blockers, and diuretics, may enhance the blood pressure-lowering effect.

Combinations containing glyceryl trinitrate and other nitrates or other vasodilators may further lower blood pressure.

Tricyclic Antidepressants / Antipsychotics / Anesthetics
Concomitant use of ACE inhibitors with certain anesthetics, tricyclic antidepressants, and antipsychotics may cause a further decrease in blood pressure (see Section 4.4).

Sympathomimetics
Sympathomimetics may reduce the blood pressure-lowering effect of ACE inhibitors.

Antidiabetics
Epidemiological studies have shown that the concomitant use of ACE inhibitors with antidiabetics (insulin, oral antidiabetics) may lead to an intensified blood-glucose-lowering effect accompanied by a risk of hypoglycemia. It is believed that this event is more likely to occur during the first weeks of combined therapy and in patients with impaired renal function.

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

Immunosuppressants, cytostatics, systemic corticosteroids, or procainamide, allopurinol
The use of fosinopril sodium in combination with immunosuppressants and/or other medications that may cause leukopenia should be avoided.

Alcohol
Alcohol enhances the blood pressure-lowering effect of fosinopril sodium.

Antacids
Antacids (e.g., aluminum hydroxide, magnesium hydroxide, dimethicone) may delay the absorption of MONOPRIL PLUS. Therefore, if concomitant administration of these agents is necessary, a 2-hour interval should be observed between doses.

Laboratory Tests
Fosinopril sodium may cause false results when measuring serum digoxin levels using the carbon absorption method (RIA Digi-Tab® Digoxin kit). Instead, other kits using antibody-coated tubes may be used. It is recommended to discontinue fosinopril sodium treatment a few days prior to measuring parathyroid gland function.

<u>Hydrochlorothiazide</u>
Alcohol, barbiturates, and narcotic analgesics
Potential increase in orthostatic hypotension may occur.

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH), or laxatives that increase motility
Hydrochlorothiazide may exacerbate electrolyte imbalances, particularly hypokalemia.

Antidiabetic agents (oral medications and insulin)
Thiazides may increase blood glucose levels; therefore, dose adjustment of antidiabetic agents may be necessary (see Section 4.4).

Calcium salts and vitamin D
When used concomitantly with thiazide-type diuretics, serum calcium levels may rise due to reduced excretion.

Digitalis glycosides
There is an increased risk of digitalis intoxication associated with thiazide-induced hypokalemia.

Cholestyramine and colestipol
These may delay or reduce the absorption of hydrochlorothiazide. Therefore, sulfonamide diuretics should be taken 1 hour before or 4–6 hours after this medication.

Vasopressors (e.g., epinephrine)
There may be a decrease in response to vasopressors; however, this decrease is not of a magnitude that would necessitate discontinuing their use.

Cytostatics (e.g., cyclophosphamide, fluorouracil, methotrexate)
Hydrochlorothiazide increases bone marrow toxicity (particularly granulocytopenia) due to reduced renal excretion of cytotoxic agents.

Gout medications (e.g., allopurinol, benzbromarone)
Since hydrochlorothiazide may increase blood uric acid levels, dosage adjustments for gout medications may be necessary. An increase in the dose of probenecid or sulfinpyrazone may be required.

Drugs that cause torsade de pointes
Caution should be exercised regarding the risk of hypokalemia when hydrochlorothiazide is used with medications that may cause torsade de pointes (e.g., antiarrhythmics, certain antipsychotics, and other medications associated with torsade de pointes).

Drugs used in surgery
The effects of non-depolarizing anesthetics and preanesthetic muscle relaxants (e.g., tubocurarine chloride and galantamine) used in surgery may be potentiated by hydrochlorothiazide; dose adjustment may be necessary. If possible, electrolyte imbalances should be monitored and corrected prior to surgery. Caution is advised when using vasopressor medications (e.g., norepinephrine) in combination with MONOPRIL PLUS. Preanesthetic and

anesthetic medications should be administered at reduced doses; if possible, hydrochlorothiazide therapy should be discontinued one week prior to surgery.

Clinical Biochemistry
Hydrochlorothiazide may cause a diagnostic interference in the bentiromide test. Thiazides may elevate serum PBI (protein-bound iodine) levels without indicating thyroid dysfunction.

Other diuretics and antihypertensive medications
The HCTZ contained in MONOPRIL PLUS may potentiate the effects of other antihypertensive medications (particularly ganglion blockers or peripheral adrenergic receptor blockers) . HCTZ may interact with diazoxide; blood glucose, uric acid levels, and blood pressure should be monitored regularly.

Clinical trial data indicate that the renin-angiotensin-aldosterone system (RAAS), dual blockade achieved through the combined use of ACE inhibitors, angiotensin II receptor blockers, or aliskiren 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-acting agent (see Sections 4.3, 4.4, and 5.1).

Fosinopril sodium/hydrochlorothiazide
Potassium-sparing diuretics and potassium supplements
ACE inhibitors reduce the potassium loss induced by diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-sparing salt substitutes may significantly increase serum potassium levels, particularly in patients with impaired renal function. If concurrent use is indicated due to established hypokalemia, this should be done with caution and with frequent monitoring of serum potassium (see Section 4.4).

Lithium
When ACE inhibitors are used concomitantly with lithium, a reversible increase in serum lithium concentrations and serum lithium toxicity has been observed. Concomitant use with diuretics further increases the risk of lithium toxicity associated with ACE inhibitors. The combined use of fosinopril sodium and hydrochlorothiazide with lithium is therefore not recommended; if the combination is deemed necessary, serum lithium levels must be closely monitored.

Endogenous prostaglandin synthesis inhibitors
In some patients, these agents may attenuate the effects of diuretics. Additionally, it has been reported that indomethacin may reduce the blood pressure-lowering effect of other ACE inhibitors (particularly in cases of low-renin hypertension). Other nonsteroidal anti-inflammatory drugs (e.g., acetylsalicylic acid) may have similar effects.

4.6 Pregnancy and lactation

General Recommendation

Pregnancy Category: D.

Women of childbearing potential/Contraception

In women of childbearing potential, appropriate contraception should be used, and an alternative treatment should be initiated prior to a planned pregnancy.

Pregnancy

MONOPRIL PLUS is contraindicated during pregnancy (see Sections 4.3 and 4.4).

ACE inhibitors

Epidemiological evidence regarding the risk of teratogenicity following ACE inhibitor use 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).

Hydrochlorothiazide

There is only limited experience regarding the use of hydrochlorothiazide during pregnancy, particularly during the first trimester. Results from animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Due to the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimesters of pregnancy may result in impaired fetoplacental perfusion and fetal and neonatal effects such as jaundice, electrolyte imbalance, and thrombocytopenia.

Due to the risk of decreased plasma volume and placental hypoperfusion without a beneficial effect on the course of the disease, hydrochlorothiazide should not be used in cases of pregnancy-induced edema, pregnancy-induced hypertension, or preeclampsia.

In cases of essential hypertension in pregnant women, hydrochlorothiazide should be used only when no other treatment is available.

Lactation:

Fosinopril sodium

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

Hydrochlorothiazide

Hydrochlorothiazide passes into breast milk in small amounts. Thiazide diuretics administered in high doses for intense diuresis may inhibit lactation. If MONOPRIL PLUS is used during lactation, the dose should be kept as low as possible.

Fertility:

The effect on fertility is unknown.

4.7 Effects on the ability to drive and use machinery

The effect on the ability to drive and use machinery is unknown.

4.8 Adverse effects

The following side effects have been observed in treatments with fosinopril sodium, other ACE inhibitors, and hydrochlorothiazide.

Adverse effects are listed in the table below according to their frequency of occurrence. The categories used for this purpose are as follows: 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
Uncommon:	Rhinitis
Rare:	Salivary gland inflammation
Not known:	Pharyngitis

(Including cysts and polyps) benign and malignant neoplasms:

Not known:	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)

Diseases of the blood and lymphatic system:

Uncommon:	Temporary decrease in hemoglobin concentration, decrease in hematocrit level
Rare:	Eosinophilia, bone marrow depression

Not known:	Lymphadenopathy, leukopenia, neutropenia, agranulocytosis, thrombocytopenia, anemia (aplastic and hemolytic forms)

Metabolic and nutritional disorders:

Very common:	Hyperglycemia, glycosuria, hyperuricemia, electrolyte disturbances (including hyponatremia and hypokalemia), increased cholesterol and triglyceride levels
Uncommon:	Anorexia, hyperkalemia
Not known:	Gout, hypochloremic alkalosis, metabolic alkalosis

Psychiatric disorders:

Uncommon:	Confusion
Rare:	Restlessness, sleep disorders
Not known:	Depression, libido disorders

Nervous system disorders:

Common:	Headache, dizziness
Uncommon:	Changes in sense of taste, tremor
Rare:	Speech disorders, memory disorders, disorientation
Not known:	Somnolence, paresthesia, hypoesthesia, syncope, fainting, stroke

Eye disorders:

Not known: visual	Choroidal effusion, acute myopia, and secondary angle-closure glaucoma, disorders, xanthopsia (yellow vision), temporary blurred vision

Ear and inner ear disorders:

Uncommon:	Ear pain
Not known:	Tinnitus, dizziness

Cardiovascular diseases:

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

Vascular diseases:

Uncommon:	Hypertension, shock, transient ischemia
Rare:	Hemorrhage, peripheral vascular diseases
Not known:	Hypotension, orthostatic hypotension, intermittent claudication, necrotizing vasculitis, facial flushing

Respiratory, chest disorders, and mediastinal diseases:

Common:	Cough
Uncommon:	Dyspnea, tracheobronchitis, sinusitis
Rare:	Epistaxis, laryngitis/hoarseness, pneumonia
Very rare:	Acute Respiratory Distress Syndrome (ARDS) (see Section 4.4)
Not known:	Nasal sinus congestion, shortness of breath, pulmonary edema, bronchospasm

Gastrointestinal disorders

Common:	Constipation, stomach irritation
Uncommon:	Dry mouth, bloating
Rare:	Oral lesions, swelling of the tongue, gas accumulation in the abdomen, difficulty swallowing
Very rare:	Intestinal angioedema, ileus
Not known:	Nausea, vomiting, diarrhea, abdominal pain, dyspepsia, gastritis, esophagitis, pancreatitis, taste disturbance

Hepatobiliary disorders:

Very rare:	Liver failure
Not known:	Hepatitis, cholestatic jaundice

Skin and subcutaneous tissue disorders:

Common:	Dermatitis
Uncommon:	Increased sweating
Rare:	Lupus erythematosus-like skin reactions, recurrence of cutaneous lupus erythematosus, anaphylactic reaction, toxic epidermal necrolysis
Not known:	Angioedema, skin rash, Stevens-Johnson syndrome, purpura, pruritus, urticaria, photosensitivity reactions, complex reactions*

Musculoskeletal disorders, connective tissue and bone diseases:

Common:	Musculoskeletal pain
Rare:	Arthritis
Not known:	Myalgia, muscle cramps, joint pain

Kidney and urinary tract disorders:

Uncommon:	Interstitial nephritis, proteinuria
Rare:	Renal dysfunction, prostate disorders
Very rare:	Acute kidney failure
Not known:	Frequent urination, dysuria, renal failure

Reproductive system and breast disorders:

Not known:	Sexual dysfunction

General disorders and conditions related to the application site:

Common:	Fatigue, weakness
Uncommon:	Fever, peripheral edema, sudden death, chest pain
Rare:	Weakness in the extremities
Not known:	Edema, chest pain, asthenia

Investigations:

Common:	Reversible increase in urinary excretion of substances (creatinine, urea)
Uncommon:	Weight gain
Rare:	Mild increase in hemoglobin levels, hyponatremia
Not known:	Abnormal liver function tests (elevated transaminases, lactate dehydrogenase, alkaline phosphatase, and bilirubin), pathological blood levels of electrolytes, uric acid, glucose, magnesium, cholesterol, triglycerides, and calcium

* A symptom complex that may include the following side effects has been described: Fever, vasculitis, myalgia, arthralgia/arthritis, evidence of antinuclear antibodies (ANA), increased erythrocyte sedimentation rate (ESR), eosinophilia and leukocytosis, exanthema, photosensitivity, or other dermatological manifestations.

In clinical trials with fosinopril/hydrochlorothiazide, no difference in the frequency of adverse effects was observed between elderly patients (>65 years) and younger patients.

Definition of selected adverse reactions
Non-melanoma skin cancer: Based on current data from epidemiological studies, a cumulative dose-dependent association has been observed between hydrochlorothiazide and non-melanoma skin cancer (see also Sections 4.4 and 5.1)

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 and Treatment

Symptoms
Depending on the amount of the overdose, the following symptoms may occur:
Severe hypotension, bradycardia, circulatory shock, electrolyte imbalances, renal failure, persistent diuresis, altered consciousness (potentially leading to coma), convulsions, paresis, cardiac arrhythmias, paralytic ileus.

Treatment

The recommended treatment in cases of overdose is intravenous infusion of normal saline solution.

The patient should be kept under close observation, preferably in an intensive care setting, after ingesting an overdose. Serum electrolytes and creatinine should be monitored frequently. Other measures, such as inducing vomiting and/or gastric lavage, are recommended to correct dehydration, electrolyte imbalances, and hypotension using established methods. If the overdose occurred recently, rapid elimination should be initiated within 30 minutes of ingestion by performing gastric lavage, administering absorbent agents, and giving sodium sulfate. If blood pressure drops, the patient should be placed in the shock position and receive rapid saline and volume replacement.

Treatment with angiotensin II should be considered. Bradycardia or severe vagal reactions should be treated with atropine. The use of a pacemaker should be considered. Fosinoprilat cannot be removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-Converting Enzyme Inhibitor and Diuretic Combinations

ATC code: C09BA09

Fosinopril sodium

Mechanism of action

Fosinopril sodium is the prodrug of fosinoprilat, a long-acting ACE inhibitor. After oral administration, it is rapidly and completely metabolized to fosinoprilat. Fosinopril sodium contains a phosphonic acid group that binds to the active binding site of the angiotensin-converting enzyme (ACE), thereby inhibiting the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II. Consequently, the resulting decrease in angiotensin II levels leads to reduced vasoconstriction and decreased aldosterone secretion; this may cause a slight increase in serum potassium and sodium and fluid loss. Generally, there are no clinically significant changes in renal plasma flow or glomerular filtration rate.

ACE inhibition also inhibits the metabolism of bradykinin, a potent vasodilator, and thus exerts a blood pressure-lowering effect; fosinopril sodium demonstrates therapeutic efficacy in patients with low renin levels.

Pharmacodynamic effects

Fosinopril sodium causes a decrease in blood pressure in patients with hypertension both while lying down and while standing, during which heart rate increases compensatorily.

In hypertension, fosinopril sodium causes a decrease in blood pressure within one hour of oral administration, with maximum effect reached 3–6 hours later. At the normal daily dose, the blood pressure-lowering effect lasts for 24 hours. In patients receiving lower doses, the effect may diminish by the end of the dose interval. Orthostatic effects and tachycardia are rare but may occur in patients with sodium deficiency or hypovolemia (see Section 4.4). In some patients, a treatment duration of 3–4 weeks may be required to achieve optimal blood pressure control. Fosinopril sodium and thiazide-type diuretics have an additive (synergistic) effect.

Clinical Efficacy and Safety
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 investigated 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 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. Considering 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 test the benefit of adding aliskiren to treatment with a standard 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.

Hydrochlorothiazide
Hydrochlorothiazide is a benzothiazide. Thiazides act directly on the kidneys by increasing the excretion of sodium chloride and, consequently, water.

Clinically, the primary site of action is the first segment of the distal tubule. There, the electron-neutral Na-Cl cotransport in the luminal cell membrane is inhibited. Potassium and magnesium are excreted in increased amounts, while calcium is excreted in decreased amounts. Hydrochlorothiazide causes reduced bicarbonate excretion, and chloride excretion exceeds sodium excretion. Metabolic acidosis may develop under the influence of hydrochlorothiazide.

Like other organic acids, hydrochlorothiazide is actively secreted in the proximal tubule. Its diuretic effect is maintained in both metabolic acidosis and metabolic alkalosis.

The mechanisms of hydrochlorothiazide's antihypertensive effects include changes in sodium balance, a decrease in extracellular water volume and plasma volume, alterations in renal vascular resistance, and a reduced response to norepinephrine and angiotensin II.
Electrolyte and water excretion with hydrochlorothiazide begins 2 hours after administration, reaches maximum effect within 3–6 hours, and persists for 6–12 hours. The antihypertensive effect first becomes apparent after 3–4 days and may persist for up to one week after discontinuation of treatment.

Non-melanoma skin cancer: Based on current data from epidemiological studies, a cumulative dose-dependent association has been observed between hydrochlorothiazide and non-melanoma skin cancer. A study included a population comprising 71,533 cases of basal cell carcinoma and 8,629 cases of squamous cell carcinoma, matched with 1,430,833 and 172,462 population controls, respectively. High-level hydrochlorothiazide use (≥50,000 mg cumulative) was associated with an adjusted odds ratio (OR; 95% confidence interval (CI): 1.29 (95% CI: 1.23–1.35) for basal cell carcinoma and 3.98 (95% CI: 3.68–4.31) for squamous cell carcinoma, as measured by the -adjusted odds ratio (OR). A clear cumulative dose-response relationship was observed for both basal cell carcinoma and squamous cell carcinoma. Another study has shown that hydrochlorothiazide exposure may be associated with lip cancer: 633 cases of lip cancer were matched with 63,067 controls using a risk-cluster sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted odds ratio (OR) of 2.1 (95% CI: 1.7–2.6); for long-term high users (~25,000 mg), the OR rises to 3.9 (3–4.9) and to 7.7 (5.7–10.5) for the highest cumulative dose (~100,000 mg).

MONOPRIL PLUS is a combination of an angiotensin-converting enzyme inhibitor (fosinopril sodium) and a diuretic (hydrochlorothiazide).

Fosinopril sodium/hydrochlorothiazide
To date, there have been no studies on cardiovascular morbidity and mortality with the use of fosinopril sodium/hydrochlorothiazide. Epidemiological studies have shown that long-term use of hydrochlorothiazide is associated with a reduction in cardiovascular morbidity and mortality.

MONOPRIL PLUS has both antihypertensive and diuretic effects. For the treatment of high blood pressure, fosinopril and hydrochlorothiazide can be used individually or in combination.

Clinical trials have shown that the blood pressure-lowering effects of fosinopril and hydrochlorothiazide are synergistic.

The maximum reduction in blood pressure was observed 2–6 hours after administration of the combination, and the antihypertensive effect was maintained for 24 hours.

Fosinopril may reduce the potassium loss associated with hydrochlorothiazide.

5.2 Pharmacokinetic properties

Fosinopril sodium

Absorption:

Fosinopril 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, although the rate of absorption may be slowed. Rapid and complete hydrolysis of the active fosinoprilat occurs in the gastrointestinal mucosa and the liver. The time to reach C_{max} is dose-dependent; C_{max} is reached approximately 3 hours after administration, and this value coincides with the maximum inhibition of the blood pressure response to angiotensin I 3–6 hours after administration. Following a single or multiple doses, pharmacokinetic parameters (C_{max}, AUC) are directly proportional to the administered dose of fosinopril.

Distribution:

Fosinoprilat binds extensively (>95%) to serum proteins. Fosinoprilat has a relatively small volume of distribution and binds extensively to proteins.

Biotransformation:

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

Elimination:

Following intravenous administration of fosinoprilat, it is excreted almost equally via the liver and kidneys. In hypertensive patients with normal renal and hepatic function receiving repeated doses of fosinopril, the elimination half-life ($t_{1/2}$) of fosinoprilat is 11.5 hours. Fosinopril is eliminated via both the liver and the kidneys.

Characteristics in patients

Renal impairment:

In patients with renal insufficiency (creatinine clearance < 80 mL/min/1.73 m^2), the total body clearance of fosinoprilat is approximately half that of patients with normal renal function, while there is no significant change 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 range) 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.

Hydrochlorothiazide
Absorption:
After oral administration, hydrochlorothiazide is absorbed from the gastrointestinal tract at a rate of approximately 80%. Systemic bioavailability is 71±15%.

Distribution:
The plasma protein binding rate of hydrochlorothiazide is 65%, and the relative volume of distribution is 0.5–1.1 L/kg.

Biotransformation:
In healthy individuals, more than 95% of hydrochlorothiazide is excreted via the kidneys.

Elimination:
The elimination half-life is 2.5 hours in patients with normal renal function. Maximum plasma levels are typically reached 2–5 hours after administration. This duration is prolonged in cases of renal dysfunction and is approximately 20 hours in patients with end-stage renal failure.

The diuretic effect becomes apparent within 1–2 hours. The duration of this effect ranges from 1 to 12 hours depending on the dose, and the blood pressure-lowering effect lasts up to 24 hours.

5.3 Preclinical safety data

Preclinical data based on conventional studies regarding safety pharmacology, toxicity with repeated administration, genotoxicity, and carcinogenic potential indicate no specific risks to humans.

In animal studies, it has been shown that angiotensin-converting enzyme inhibitors have a negative effect on late fetal development, leading to fetal mortality and congenital malformations, particularly skull deformities. Similarly, fetotoxicity, intrauterine growth retardation, and persistent ductus arteriosus have been observed. These developmental abnormalities are likely caused in part by the ACE inhibitor's effect on the fetal renin-angiotensin system, in part by ischemia, and in part by the hypotension observed in the mother,

leading to a decrease in fetal-placental circulation and in the fetus's oxygen and nutrient supply (see Section 4.6).

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Anhydrous lactose (made from cow's milk)
Lactose monohydrate (derived from cow's milk)
Sodium croscarmellose
Povidone K30
Sodium stearyl fumarate
Yellow iron oxide
Red iron oxide

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

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