SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KAPTORIL® 25 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each tablet contains 25 mg of captopril.

Excipient(s):

Lactose monohydrate 51.25 mg

For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, slightly biconvex tablets, one side is notched in the middle, the other side has the straight with a homogeneous appearance.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

KAPTORIL is indicated in the treatment of hypertension and chronic heart failure with reduced systolic ventricular function.

4.2 Posology and method of administration

Posology / Frequency of administration and duration:

KAPTORIL should be taken 1 hour before meals.

In hypertension: Treatment is started with 25 mg of KAPTORIL given two or three times daily. If an adequate response is not achieved within 2 weeks, the dose should be increased to 100–150 mg per day. KAPTORIL can be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

In patients with a highly active renin-angiotensin-aldosterone system (hypovolemia, renovascular hypertension, cardiac decompensation), an initial single dose of 6.25–12.5 mg is recommended and this treatment method should be performed under medical supervision. The dose should then be continued twice daily. If necessary, the daily dose may be increased to 50 mg or 100 mg, given once or twice daily.

In heart failure: Before initiating therapy, it should be determined whether the patient is already on diuretics. In patients treated with diuretics who may be hyponatremic or hypovolemic, treatment should be started with 6.25 mg or 12.5 mg captopril two or three times daily. This approach minimizes the risk of hypotension. Switching to the maintenance dose (75–150 mg/day) should be adjusted according to the patient's response to treatment. The maximum daily dose is 150 mg and must not be exceeded. Captopril should be used in combination with diuretics and digitalis, and the patient should remain under medical supervision.

Method of administration:

KAPTORIL is for oral use.

Additional Information on Special Populations:

Renal/Hepatic impairment:

Since captopril is primarily excreted by the kidneys, lower doses or extended dosing intervals may be required in patients with impaired renal function. Treatment with captopril should be initiated with low doses and gradually increased every 2 weeks. Once an adequate response is achieved, the dose should be gradually reduced to determine the minimum effective dose.

Recommended captopril doses based on creatinine clearance in patients with renal impairment:

Creatinine clearance (ml/min/1.73 m²)	Initial daily dose (mg)	Maximum Daily Dose (mg)
> 40	25 – 50	150
21 – 40	25	100
10 – 20	12,5	75
< 10	6,25	37,5

In patients with renal impairment, low doses should be administered every 8–12 hours, and renal function and leukocyte counts should be closely monitored during treatment.

In patients undergoing moderate hemodialysis with 20–50% dialyzability, the dose should be administered after dialysis or an additional dose are applied at rates between 25% and 35%.

In patients undergoing peritoneal dialysis, no additional dose is required.

If a diuretic is needed in patients with impaired renal function, furosemide or a similar diuretic is preferred.

There is no data available on patients with hepatic impairment.

Pediatric population:

KAPTORIL is not recommended for use in children for the treatment of high blood pressure. However, your doctor may prescribe a lower dose based on your child's weight.

The initial dose in children is 0.3 mg per kg of body weight, and your doctor may adjust the dose depending on the treatment response.

In children with impaired renal function, the initial dose is 0.15 mg per kg of body weight. Captopril is generally administered three times daily in children, but the dose and dosing interval should be determined according to the patient's needs.

Geriatric population:

There are no data available regarding this patient population.

4.3 Contraindications

KAPTORIL is contraindicated in patients who are hypersensitive to any component of the preparation or to other ACE inhibitors (those who have experienced angioedema during ACE inhibitor treatment), in patients with hereditary or idiopathic angioneurotic edema, and during pregnancy and lactation.

4.4 Special warnings and precautions for use

Hypotension: Hypotension has rarely been observed in uncomplicated hypertensive patients. The likelihood of symptomatic hypotension is higher in hypertensive patients who have experienced fluid and/or sodium loss due to intensive diuretic therapy, dietary salt restriction, diarrhea, vomiting, or hemodialysis. Volume and/or sodium depletion should be corrected prior to initiating ACE inhibitor therapy, and a lower starting dose should be considered.

In patients with heart failure, the risk of hypotension is higher, and it is recommended to start treatment with a lower initial dose of the ACE inhibitor. Caution is advised when increasing the dose of captopril or diuretics in patients with heart failure.

As with all antihypertensive agents, excessive blood pressure reduction in patients with ischemic cardiovascular or cerebrovascular disease may increase the risk of myocardial infarction or stroke. If hypotension occurs, the patient should be placed in a supine position. Intravenous normal saline may be required for water (volume) repletion.

Renal hypertension: In patients with bilateral renal artery stenosis or artery stenosis in a solitary functioning kidney, the risk of hypotension and renal failure is increased when treated with ACE inhibitors. Renal impairment may occur with only slight changes in serum creatinine. Treatment should be initiated under close medical supervision, with low doses, careful titration, and monitoring of renal function.

Renal impairment: In cases of renal insufficiency (creatinine clearance ≤ 40 ml/min), the initial dose of captopril should be adjusted according to the patient's creatinine clearance and subsequently based on the patient's response to treatment. Routine monitoring of potassium and creatinine levels is part of standard medical practice in these patients.

Angioedema: Angioedema of the extremities, face, lips, mucous membranes, tongue, glottis, or larynx may occur in patients treated with ACE inhibitors, especially during the first weeks of treatment. However, in rare cases, severe angioedema may develop after long-term treatment with ACE inhibitors. Treatment must be discontinued immediately. Angioedema involving the tongue, glottis, or larynx may be fatal. Emergency treatment is essential. The patient should be hospitalized and monitored for at least 12 to 24 hours and discharged only after complete resolution of symptoms.

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is persistent and resolves after discontinuation of therapy.

Hepatic impairment: Rarely, ACE inhibitors have been associated with a syndrome that begins with cholestatic hepatitis and progresses to fulminant hepatic necrosis, (sometimes) resulting in death. The mechanism of this syndrome is not understood. ACE inhibitor therapy should be discontinued in patients who develop hepatitis or marked elevations in hepatic enzymes, and appropriate medical follow-up should be initiated.

Hyperkalemia: Increases in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. Patients at risk for developing hyperkalemia include those with renal insufficiency, diabetes mellitus, or those using potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs associated with increased serum potassium (e.g., heparin) at the same time . If the above-mentioned agents are used concomitantly, regular monitoring of serum potassium is recommended.

Lithium: Concurrent use of captopril and lithium is not recommended.

Aortic and mitral valve stenosis / obstructive hypertrophic cardiomyopathy: ACE inhibitors should be used with caution in patients with left ventricular valvular and outflow tract obstruction. In patients with cardiogenic shock and hemodynamically significant obstruction, the use of ACE inhibitors should be avoided.

Neutropenia / Agranulocytosis: Neutropenia/agranulocytosis, thrombocytopenia, and anemia have been reported in patients receiving ACE inhibitors, including captopril. Neutropenia rarely occurs in patients with normal renal function and no other complicating factors. Captopril should be used with extreme caution in patients with collagen vascular disease, those receiving immunosuppressive therapy, those being treated with allopurinol or procainamide, or when these factors coexist—especially in the presence of pre-existing renal impairment. Some of these patients have developed serious infections, and in some cases, the infections did not respond to intensive antibiotic therapy.

If captopril is used in such patients, a white blood cell count and differential count should be performed before treatment, every two weeks during the first three months of therapy, and periodically thereafter. Patients should be advised to report any signs of infection (e.g., sore throat, fever) when differential white blood cell count is required, during treatment. If neutropenia is diagnosed or suspected, captopril and any concomitant drugs should be discontinued.

In most patients, neutrophil counts return to normal rapidly after discontinuation of captopril.

Proteinuria: Proteinuria may occur, particularly in patients with existing renal impairment or those receiving relatively high doses of ACE inhibitors.

More than 1 g/day of total urinary protein has been observed in approximately 0.7% of patients receiving captopril. The majority of these patients had evidence of pre-existing renal disease or were receiving relatively high doses of captopril (more than 150 mg/day), or both. Nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, whether or not captopril treatment was continued, proteinuria diminished or disappeared within six months. Renal function parameters such as BUN and creatinine were rarely altered in patients with proteinuria.

In patients with pre-existing renal disease, urine protein should be measured regularly before and during treatment (using a dipstick test on the first morning urine sample).

Anaphylactoid reactions during desensitization: In patients receiving desensitization treatment with Hymenoptera venom while also taking another ACE inhibitor, sustained, life-threatening anaphylactoid reactions have rarely been reported. In the same patients, these reactions ceased when the ACE inhibitor was temporarily discontinued but recurred upon re-administration. Therefore, caution is advised in patients undergoing such desensitization procedures while being treated with ACE inhibitors.

Anaphylactoid reactions during high-flux dialysis / exposure to lipoprotein apheresis membranes: Anaphylactoid reactions have been reported in patients undergoing hemodialysis with high-flux dialysis membranes or exposed to low-density lipoprotein apheresis using dextran sulfate absorption. In such patients, alternative dialysis, membranes or a different class of medication should be considered.

Surgical intervention / Anesthesia: During surgical procedures and anesthesia, patients should be carefully monitored for the possibility of hypotension. If hypotension occurs, treatment should be with volume expansion.

Diabetic patients: In diabetic patients previously treated with oral antidiabetics or insulin, glycemia levels should be closely monitored during the first month of treatment with an ACE inhibitor.

Lactose: KAPTORIL 25 mg tablet contains 51.25 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance or glucose-galactose malabsorption should not use this medicine.

Ethnic differences: As with other angiotensin-converting enzyme inhibitors, captopril is less effective in lowering blood pressure in black patients compared to white patients. This may be due to the higher prevalence of low-renin states in the black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction

Potassium-sparing diuretics or potassium supplements: ACE inhibitors reduce diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant changes in serum potassium. If co-administration is indicated due to diagnosed hypokalemia, caution should be exercised and serum potassium should be frequently monitored.

Diuretics (thiazide or loop diuretics): Previous treatment with high-dose diuretics may increase the risk of fluid depletion and hypotension at the beginning of captopril therapy (see section 4.4). Discontinuation of the diuretic, increasing fluid or salt intake, or initiating therapy with a low dose of captopril may reduce hypotensive effects. However, studies with hydrochlorothiazide or furosemide have shown no clinically significant drug interactions.

Other antihypertensive agents: Captopril has been safely used in combination with commonly used antihypertensive agents (e.g., beta-blockers and long-acting calcium channel blockers). Concurrent use of these agents may enhance the hypotensive effects of captopril. Treatment with nitroglycerin and other nitrates or other vasodilators should be administered with caution.

Treatment of acute myocardial infarction: In patients with myocardial infarction, captopril may be used together with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers, and/or nitrates.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of lithium and ACE inhibitors. The use of thiazide diuretics may further increase the risk of lithium toxicity and may potentiate the already elevated risk when combined with ACE inhibitors. The use of lithium with captopril is not recommended; however, if the combination is deemed necessary, serum lithium levels should be closely monitored.

Tricyclic antidepressants / Antipsychotics: ACE inhibitors may enhance the hypotensive effects of certain tricyclic antidepressants and antipsychotics. Postural hypotension may occur.

Allopurinol, procainamide, cytostatic or immunosuppressive agents: Co-administration with ACE inhibitors, may increase the risk of leukopenia when ACE inhibitors are used in high doses.

Non-steroidal anti-inflammatory drugs (NSAIDs): While non-steroidal anti-inflammatory drugs (NSAIDs) and ACE inhibitors may have additive effects on increasing serum potassium, they may also reduce renal function. These effects are usually reversible. Acute renal failure may occur particularly in patients with pre-existing compromised renal function, such as the elderly or dehydrated individuals. Chronic use of NSAIDs may reduce the antihypertensive effect of ACE inhibitors.

Sympathomimetics: May reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored.

Antidiabetics: Pharmacological studies have shown that ACE inhibitors, including captopril, may enhance the blood glucose-lowering effects of oral antidiabetics such as sulfonylureas and insulin. In rare cases where this interaction occurs, the dose of the antidiabetic agent may need to be reduced during concomitant treatment with ACE inhibitors.

4.6 Fertility, pregnancy and lactation

General principles

Pregnancy category is C for the first trimester and D for the second and third trimesters.

Women of childbearing potential / Birth control (Contraception)

Animal studies are insufficient with regard to the effects on pregnancy and/or embryonal/fetal development and/or parturition and/or postnatal development (see section 5.3). The potential risk to humans is unknown.

Appropriate birth control method for women of childbearing potential

Due to the lack of adequate data on the use of captopril in pregnant women, it is recommended that women of childbearing potential use appropriate methods of contraception.

Pregnancy

First trimester:

The use of ACE inhibitors during pregnancy may cause fetal and neonatal morbidity and death. The medication should be discontinued immediately upon recognition of pregnancy.

KAPTORIL should not be used during pregnancy unless necessary.

Second and third trimesters:

Use of ACE inhibitors during the second and third trimesters of pregnancy can result in fetal and neonatal morbidity and death. The medication must be discontinued immediately when pregnancy is detected. KAPTORIL is contraindicated during the second and third trimesters. After exposure to captopril during these periods, cases of oligohydramnios, hypotension, oliguria, anuria, impaired skull ossification, reversible or irreversible renal impairment, and death in newborns have been reported. Use of the drug during this time may result in premature birth and low birth weight.

Lactation Period

As captopril passes into breast milk, nursing mothers should either discontinue the medication or stop breastfeeding. KAPTORIL is contraindicated during the lactation period.

4.7 Effects on ability to drive and use machines

Due to its effects on blood pressure, driving or operating machinery is not recommended while taking this medication.

4.8 Undesirable effects

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); unknown (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very rare: Neutropenia, agranulocytosis, leukopenia, anemia, thrombocytopenia, pancytopenia, autoimmune diseases and/or ANA values positivity, eosinophilia, lymphadenopathy.

Metabolism and nutrition disorders:

Rare: Anorexia

Very rare: Hyperkalemia, hypoglycemia

Psychiatric disorders:

Common: Sleep disturbances

Very rare: Confusion, depression.

Nervous system disorders:

Common: Taste disturbance, dizziness

Rare: Drowsiness, headache and paresthesia

Very rare: Cerebrovascular events including stroke and syncope

Eye disorders

Very rare: Blurred vision.

Cardiac disorders

Uncommon: Tachycardia or tachyarrhythmia, angina pectoris, palpitations

Very rare: Cardiac arrest, cardiogenic shock.

Vascular disorders

Uncommon: Hypotension, Raynaud's syndrome, flushing, pallor.

Respiratory, thoracic, and mediastinal disorders

Common: Dry and irritating cough, dyspnea

Very rare: Bronchospasm, rhinitis, allergic alveolitis, eosinophilic pneumonia.

Gastrointestinal disorders

Common: Nausea, vomiting, gastric discomfort, abdominal pain, diarrhea, constipation, dry mouth

Rare: Stomatitis / aphthous ulcers

Very rare: Glossitis, peptic ulcer, pancreatitis.

Hepatobiliary disorders

Very rare: Liver function impairment and cholestasis (including jaundice), hepatitis including necrosis, increase in liver enzymes and bilirubin.

Skin and subcutaneous tissue disorders

Common: Rash with or without itching, alopecia

Rare: Angioedema

Very rare: Urticaria, Stevens-Johnson syndrome, erythema multiforme, photosensitivity, erythroderma, pemphigoid reactions, and exfoliative dermatitis.

Musculoskeletal, connective tissue and bone disorders

Very rare: Arthralgia, myalgia.

Renal and urinary disorders

Rare: Renal impairment such as renal failure, polyuria, oliguria, increased urinary frequency

Very rare: Nephrotic syndrome.

Reproductive system and breast disorders:

Very rare: Impotence, gynecomastia.

General disorders:

Rare: Chest pain, fatigue, malaise

Very rare: Fever

Investigations:

Very rare: Proteinuria, eosinophilia, increased serum potassium, decreased serum sodium, increased BUN, serum creatinine and bilirubin, decreased hemoglobin level, hematocrit, leukocyte and platelet, positive ANA titer, elevated ESR.

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 related to overdose include severe hypotension, shock, stupor, bradycardia, electrolyte disturbances, and renal failure.

If exposure is recent, measures should be taken to prevent absorption (e.g., gastric lavage, administration of adsorbents and sodium sulfate within 30 minutes after exposure) and to eliminate the absorbed drug. If hypotension occurs, the patient should be placed in a shock position and given salt and volume supplementation. Angiotensin II therapy should be considered. Bradycardia or pronounced vagal reactions should be treated with atropine. The use of a pacemaker may be considered.

Captopril can be removed from circulation by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin-Converting Enzyme (ACE) Inhibitors

ATC code: C09AA01

The active substance of KAPTORIL, captopril, is a potent competitive inhibitor of the angiotensin-converting enzyme (ACE). The drug acts by suppressing the renin-angiotensin-aldosterone system. Renin is an enzyme synthesized in the kidneys. Once released into the bloodstream, it plays a role in the conversion of angiotensinogen to angiotensin I. Angiotensin I is then converted to angiotensin II by ACE. Angiotensin II is a potent vasoconstrictor and also stimulates the secretion of aldosterone from the adrenal cortex, leading to sodium and fluid retention. Captopril inhibits ACE and thus prevents the conversion of angiotensin I to angiotensin II. Captopril is also effective in hypertensive cases with low levels of renin, although the mechanism of this effect is unknown.

ACE is identical to kininase II. Kininase II degrades bradykinin, a vasodepressive peptide. By inhibiting this enzyme, captopril leads to increased levels of bradykinin or prostaglandin E2.

ACE inhibition prevents the conversion of angiotensin I to the potent vasopressor angiotensin II, resulting in peripheral vasodilation; accompanied by an increase in plasma renin activity and a decrease in aldosterone secretion. Thus, sodium and fluid retention are also reduced, producing an antihypertensive effect.

Captopril reduces peripheral arterial resistance in hypertensive patients without changing or increasing cardiac output. Following the use of captopril, an increase in renal blood flow has been observed. A maximum reduction in blood pressure occurs 60-90 minutes after oral administration of captopril.The duration of the effect is dose-dependent. The blood pressure-lowering effect appears gradually. To achieve maximum therapeutic effect, treatment may need to be continued for several weeks. Captopril and thiazide-type diuretics produce an additive effect on lowering blood pressure. The additive effects of captopril and beta-blockers are lesser.

5.2 Pharmacokinetic properties

General Properties

Absorption:

Captopril is rapidly absorbed when administered orally, with at least 75% being absorbed, and peak plasma concentration is reached 60–90 minutes after intake. Taking it with food reduces its absorption by 30–40%. Therefore, captopril should be taken 1 hour before meals.

Distribution:

Approximately 25–30% of circulating drug binds to plasma proteins. The biological half-life is about 2–5 hours.

Biotransformation:

Captopril is metabolized in the liver.

Elimination:

95% of the absorbed dose is excreted in the urine within 24 hours. Of the absorbed drug, 40–50% is excreted unchanged, and the remainder as captopril disulfide and captopril-cysteine disulfide compounds.

Linearity/non-linearity:

No data available.

5.3 Preclinical safety data

The active substance contained in this product has been used in clinical practice for many years. The studies on it have been completed. Possible adverse effects related to its use are included in the relevant sections (4.4, 4.6, 4.8, 4.9).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Colloidal silicon dioxide

Microcrystalline cellulose

Starch

Stearic acid

6.2. Incompatibilities

N.A

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at room temperature below 30°C. Protect from moisture.

6.5 Nature and contents of container

Blisters containing 10 tablets, with one side made of transparent PVDC and the other side of printed aluminum foil.

Each carton contains 50 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

139/54

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15.07.1986

Date of latest renewal: 06.04.2004

10. DATE OF REVISION OF THE SPC