SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Captopril Denk 25

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: captopril
Each tablet contains 25 mg captopril.
Excipient with known effect: Each tablet contains 52 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to off-white, round, flat tablets with facet, with a break-line on one side and the inscription “25” on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Captopril Denk 25 is used
- in the treatment of hypertension,
- in the treatment of chronic cardiac insufficiency with reduction of systolic ventricular function, in combination with diuretics and, when appropriate, digitalis and betablockers (see sections 4.3, 4.4, 4.5 and 5.1).

4.2 Posology and method of administration

Posology
The dosage should be adjusted individually and according to blood pressure response. The recommended maximum daily dose is 150 mg.

Hypertension
The recommended initial dose is 25-50 mg daily, administered in two doses. In order to achieve the desired therapeutic effect, the dosage may be gradually increased to 100–150 mg daily, administered in two doses, at 2-week intervals depending on necessity.
Captopril may be administered alone or in combination with other antihypertensive agents, particularly with thiazide diuretics (see sections 4.3, 4.4, 4.5 and 5.1). When antihypertensive medication such as thiazide diuretics are administered concomitantly, a once daily dosage scheme may be indicated.
In patients with a very active renin angiotensin aldosterone system (hypovolaemia, renovascular hypertension, cardiac decompensation), a single dose of 6.25 mg or 12.5 mg is preferable as an initial dose. The treatment should be commenced preferably under careful medical supervision, and the dosages then administered two times a day. The dosage can be gradually increased to 50 mg daily and, if necessary, to 100 mg daily, given in one or two doses.

Cardiac insufficiency
Treatment with captopril should be started under careful medical supervision.
The initial dose generally ranges from 6.25 mg to 12.5 mg captopril two or three times a day. The dose should only be increased gradually depending on the patient's individual response to therapy; the maintenance dose is 75 – 150 mg captopril daily, divided up into several doses. The maximum dose is 150 mg captopril daily, divided up into several doses.
The dosage should be increased gradually, and there should be an interval of at least 2 weeks in order to establish the patient's response.

Impaired kidney function
As captopril is excreted primarily via the kidneys, the dosage should be reduced or dosage intervals should be prolonged in patients with impaired kidney function. When concomitant diuretic therapy is required in patients with severe kidney failure, a loop diuretic (e.g. furosemide) rather than a thiazide diuretic is preferred for use with captopril.
The following daily doses are recommended for patients with impaired kidney function in order to avoid an accumulation of captopril:

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

Elderly patients
In elderly patients with impaired renal function who may also suffer from other organ dysfunction, a low initial dose (6.25 mg two times a day) should be considered when administering captopril or other antihypertensive agents (see above and section 4.4). The dosage should be increased gradually according to blood pressure response until the minimal effective dosage is achieved.

Children and adolescents
The efficacy and innocuousness of captopril has not been fully established in this patient group. Treatment with captopril should be initiated in children and adolescents under careful medical supervision. The initial dose of captopril is approx. 0.3 mg/kg body weight. The initial dose should only be 0.15 mg captopril/kg body weight in patients requiring particular precautionary measures (children with kidney failure, premature infants, neonates and infants, as their renal function is not comparable to that of older children or adults). In general, captopril is administered to children three times a day. However, the dosage and dosage interval should be adjusted according to the individual response of the patient.

Method of administration
Captopril Denk 25 may be taken before, during and after mealtimes.

4.3 Contraindications

- Hypersensitivity to the active substance, to any other ACE inhibitor or to any of the excipients listed in section 6.1
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Concomitant use of captopril with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Captopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).
- Second and third trimester of pregnancy (see sections 4.4 and 4.6)

4.4 Special warnings and precautions for use

Hypotension
Hypotension is rarely observed in patients with uncomplicated hypertension. Symptomatic hypotension is more likely to be seen in salt/volume depleted patients resulting from vigorous diuretic therapy, low salt diet, diarrhoea, vomiting or haemodialysis. Prior to administering an ACE inhibitor, fluid and/or salt depletion should be corrected and a lower initial dose considered.
Patients with heart failure are more at risk of developing hypotension, and a low initial dose of an ACE inhibitor is therefore recommended. Caution should always be exercised in patients suffering from heart failure whenever the captopril or diuretic dose is increased.
As with all antihypertensive agents, an extensive fall in blood pressure may increase the risk of occurrence of myocardial infarction or stroke in patients with ischaemic cardiovascular or cerebrovascular disease. If hypotension develops, the patient should be placed in the supine position. Intravenous hydration with physiological saline may be indicated.

Renovascular hypertension
Bilateral renal artery stenosis or unilateral renal artery stenosis in patients with one functional kidney are at increased risk of developing hypotension and kidney failure when receiving ACE inhibitors. Loss of renal function may be associated with only moderate changes in serum creatinine. In such patients, therapy should be commenced at low doses under careful medical supervision, the dosage should be adjusted carefully and gradually, and renal function should be monitored.

Impaired renal function
In patients with impaired renal function (creatinine clearance ≤ 40 ml/min), the initial dose of captopril should be adjusted according to the individual creatinine clearance (see section 4.2), and subsequently calculated according to the patient's response to treatment. In such patients, routine evaluation of potassium and creatinine is normal medical practice.

Hypersensitivity/angioedema
Particularly during the first weeks of treatment, patients receiving treatment with ACE inhibitors may develop angioedema of the extremities, face, lips, mucosa, tongue, glottis or larynx. In rare cases, however, severe angioedema may even develop after long-term therapy with an ACE inhibitor. The treatment should be discontinued immediately. Angioedema with involvement of the tongue, glottis or larynx can be fatal. Emergency measures should be initiated. The patient should be admitted to hospital and kept under medical supervision for at least 12 to 24 hours, and should not be discharged until all symptoms have abated completely.

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of captopril. Treatment with captopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

Cough
There have been reports of a cough in association with ACE inhibitors. The cough is generally non-productive, persistent and disappears once the treatment has been discontinued.

Liver failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis, which can be fatal. The mechanism of this syndrome is not

understood. Patients receiving ACE inhibitors who develop jaundice or exhibit marked elevations of hepatic enzymes, should discontinue ACE inhibitors and receive appropriate medical supervision.

Serum potassium
ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or cotrimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

Lithium
Co-administration of lithium and captopril is not advisable.

Aortic and mitral valve stenosis/obstructive hypertrophic cardiomyopathy
ACE inhibitors should be administered with caution to patients suffering from left ventricular valve and outflow obstruction, and should not be administered to patients suffering from cardiogenic shock and haemodynamically significant obstruction.

Neutropenia/Agranulocytosis
There have been reports of neutropenia/agranulocytosis, thrombocytopenia and anaemia in patients receiving treatment with ACE inhibitors, including captopril. Neutropenia rarely occurred in clinically stable patients with normal renal function. Captopril should be administered with the utmost caution to patients suffering from collagen vascular disease, patients receiving immunosuppressive agents, allopurinol or procainamide or patients with a combination of these complicating factors, particularly those with impaired renal function.
Some of these patients developed severe infections, which sometimes did not respond to intensive antibiotic therapy.
When administering captopril to such patients, it is advisable to evaluate the white blood cell and differential counts prior to starting treatment and at 2-week intervals during the first 3 months of therapy, then periodically. During treatment all patients should be instructed to inform their physician of any signs of an infection (e.g. sore throat, fever). In such cases, the differential white blood cell count should be evaluated. If neutropenia (less than 1000/mm^3 neutrophils) is detected or suspected, captopril and other concomitant medication (see section 4.5) should be discontinued.
In most patients, the neutrophil count promptly returns to normal once captopril has been discontinued.

Proteinuria
Proteinuria may occur, particularly in patients with pre-existing renal impairment or in those receiving relatively high doses of ACE inhibitors.
Total urinary protein greater than 1 g per day was observed in approx. 0.7 % of patients receiving captopril. The majority of patients had evidence of prior renal disease or were receiving relatively high doses of captopril (more than 150 mg/day) or both. Nephrotic syndrome occurred in approx. one fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 weeks, regardless of whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.
Urinary protein should be determined in patients with evidence of prior renal disease before commencing treatment, and then periodically (test strips in first morning urine).

Anaphylactoid reactions during desensitising treatment
In rare instances, persistent life-threatening anaphylactoid reactions have been reported in patients undergoing desensitising treatment with hymenoptera venom while receiving ACE inhibitors. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they

reappeared upon inadvertent rechallenge. Caution should therefore be exercised in patients undergoing such a desensitising treatment while receiving ACE inhibitors.

Anaphylactoid reactions to high-flux dialysis/lipoprotein apheresis membrane exposure
Anaphylactoid reactions have been reported in patients who underwent dialysis with high-flux membranes or low-density lipoprotein apheresis with dextran sulfate. In such patients, the use of another dialysis membrane or another class of drugs should be considered.

Surgery/Anaesthesia
Hypotension may occur in patients undergoing major surgery or in those receiving treatment with anaesthetics that are known to reduce blood pressure. If hypotension does occur, it can be corrected by volume expansion.

Diabetics
Blood sugar should be monitored closely in diabetics who have been treated with oral antidiabetic agents or insulin in the past, particularly during the first month of treatment with ACE inhibitors.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Ethnic differences
Just like other angiotensin-converting enzyme inhibitors, captopril is less effective in reducing blood pressure in black patients than in non-blacks. This could be related to the fact that decreased renin levels are more common in the black population with hypertension.

This medicine contains lactose.
Patients with rare hereditary problems of galactose intolerance, of total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Medicines increasing the risk of angioedema
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).
Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with captopril. Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when captopril is co-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 like amiloride. Therefore, the combination of captopril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Ciclosporin
Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

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

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may lead to fluid depletion and the risk of hypotension at the commencement of captopril therapy (see section 4.4). The hypotensive effect can be diminished by discontinuing the diuretic, correcting fluid and salt depletion or by initiating therapy with a low dose of captopril. However, specific studies with hydrochlorothiazide and furosemide revealed no clinically significant interactions with other medicines.

Other antihypertensive agents
Captopril has certainly been administered with other commonly used antihypertensive agents such as beta blockers or calcium channel blockers with long-term effect. Concomitant administration of these substances may augment the antihypertensive effect of captopril. Caution should be exercised when nitroglycerine and other nitrates or other vasodilators are co-administered with captopril.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4, and 5.1).

Treatment of acute myocardial infarction
Captopril can be used concomitantly with acetylsalicylic acid (in cardiology doses), thrombolytic agents, beta blockers and/or nitrates in patients with myocardial infarction.

Lithium
There have been reports of reversible increases in serum lithium and toxicity in patients receiving concomitant lithium and ACE inhibitor therapy. Concomitant administration of thiazide diuretics can increase the risk of lithium toxicity and may potentiate the already increased risk of lithium toxicity associated with ACE inhibitors. Lithium and captopril should not be co-administered. However, if concomitant administration of both preparations is required, serum lithium should be monitored carefully (see section 4.4).

Tricyclic antidepressants /antipsychotic agents
ACE inhibitors may potentiate the hypotensive effect of certain tricyclic antidepressants and antipsychotic agents (see section 4.4). Orthostatic hypotension may occur.

Allopurinol, procainamide, cytostatics or immunosuppressive agents
Concomitant administration of ACE inhibitors may increase the risk of leukopenia, particularly if the latter is administered in higher doses than the dose now recommended.

Non-steroidal anti-inflammatory drugs
It has been reported that non-steroidal anti-inflammatory drugs (NSAIDs) and ACE inhibitors increase

serum potassium in an additive process, while renal function may be diminished. These effects are reversible in principle. In rare cases, acute renal failure may occur, particularly in patients with impaired renal function, e.g. in the case of elderly or dehydrated patients. Long-term use of NSAIDs can reduce the hypotensive effect of ACE inhibitors.

Sympathomimetic agents
They can reduce the hypotensive effect of ACE inhibitors; the patients should be monitored carefully.

Antidiabetic agents
Pharmacological studies have shown that the hypoglycaemic effect of insulin and oral antidiabetics, such as sulfonyl urea, may be potentiated by the use of ACE inhibitors, including captopril. If this extremely rare interaction does occur, it may be necessary to reduce the dosage of antidiabetic medication during concomitant treatment with ACE inhibitors.

Clinical chemistry
Captopril can produce a false positive urine test for acetone.

4.6 Pregnancy and lactation

Pregnancy

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
ACE inhibitor therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also sections 4.3 and 4.4).

Lactation
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of captopril in breast-feeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.
In the case of an older infant, the use of captopril in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

Just like other antihypertensive agents, captopril may impair the ability to drive and operate machinery. This applies in particular to the initial period of treatment, a rise in dosage as well as in combination with alcohol. These effects, however, depend on individual susceptibility.

4.8 Undesirable effects

The following frequency scale is used as a basis in the assessment of adverse drug reactions:

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)

Adverse drug reactions that were reported in association with captopril and/or treatment with another ACE inhibitor are as follows:

Blood and lymphatic system disorders
Very rare: neutropenia/agranulocytosis, pancytopenia (see section 4.4), particularly in patients with renal dysfunction (see section 4.4), anaemia (including aplastic and haemolytic), thrombocytopenia, lymphadenopathy, eosinophilia, autoimmune diseases and/or positive ANA titer.

Metabolism and nutrition disorders
Rare: anorexia.
Very rare: hypoglycaemia, hyperkalaemia (see section 4.4).

Psychiatric disorders
Common: sleep disorders.
Very rare: confusion, depression.

Nervous system disorders
Common: taste impairment, dizziness.
Rare: drowsiness, headache and paraesthesia.
Very rare: cerebrovascular incidents, 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 (see section 4.4), Raynaud's syndrome, flush, pallor.

Respiratory, thoracic and mediastinal disorders
Common: dry irritating (non-productive) cough (see section 4.4) and dyspnoea.
Very rare: bronchospasm, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders
Common: nausea, vomiting, gastric irritation, abdominal pain, diarrhoea, constipation, dry mouth.
Rare: stomatitis, aphthous ulcerations.
Very rare: glossitis, peptic ulcer, pancreatitis.

Hepatobiliary disorders
Very rare: impaired hepatic function and cholestasis (including jaundice), hepatitis including necrosis, elevated liver enzymes and bilirubin.

Skin and subcutaneous tissue disorders
Common: pruritus with or without rash, rash and alopecia.
Uncommon: angioedema (see section 4.4).

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

Musculoskeletal and connective tissue disorders
Very rare: myalgia, arthralgia.

Renal and urinary disorders
Rare: renal function disorders including renal failure, polyuria, oliguria, increased urine frequency.
Very rare: nephrotic syndrome.

Reproductive system and breast disorders
Very rare: impotence, gynaecomastia.

General disorders and administration site conditions
Uncommon: chest pain, fatigue, malaise.
Very rare: fever.

Investigations
Very rare: proteinuria, eosinophilia, increase in serum potassium, decrease of serum sodium, elevation of BUN, serum creatinine and serum bilirubin, decrease in haemoglobin, haematocrit, leucocytes, thrombocytes, positive ANA titre, elevated erythrocyte sedimentation rate.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms of an overdose are severe hypotension, shock, stupor, bradycardia, electrolyte imbalance and renal failure.
If the medication has been taken only recently, measures should be taken to prevent absorption (e.g. gastric lavage, administration of adsorbent materials and sodium sulfate within 30 minutes of intake) and accelerate elimination. If hypotension occurs, the patient should be placed in the shock position while salt substitutes and fluids should be administered rapidly. Treatment with angiotensin II should be considered. Bradycardia or pronounced vagal stimulation should be treated by administering atropine. Pacemaker therapy can be considered. Captopril can be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor
ATC Code: C09AA01

Mechanism of action
Captopril is a highly specific competitive inhibitor of the angiotensin I-converting enzyme (ACE inhibitor).
The beneficial effect of ACE inhibitors appears to result primarily from suppression of the plasma renin-angiotensin-aldosterone system. Renin, an endogenous enzyme synthesized by the kidneys, is released into the circulation where it is responsible for converting angiotensinogen into angiotensin I, a relatively inactive decapeptide. Angiotensin I is subsequently converted into angiotensin II by the angiotensin-converting enzyme, a peptidyl-dipeptidase. Angiotensin II is a potent vasoconstrictor substance that is responsible for arterial vasoconstriction while also raising blood pressure and

stimulating aldosterone secretion from the adrenal glands. Inhibition of ACE causes a decrease in plasma concentration of angiotensin II and this in turn contributes to reduced vasopressor activity as well as a decrease in aldosterone secretion. Although the latter is slight it may still lead to a small increase in serum potassium along with sodium and fluid depletion. Plasma renin activity increases as a result of loss of negative feedback of angiotensin II on renin secretion.
The conversion enzyme is also responsible for the breakdown of the kinin peptide, bradykinin, which is a potent vasodilator, into an inactive metabolite. ACE inhibition therefore leads to increased activity of the circulating and local kallikrein-kinin system, which contributes to peripheral vasodilation by activating the prostaglandin system. This mechanism may play a part in the antihypertensive effect of ACE inhibitors and may be responsible for certain adverse reactions.

Pharmacodynamic effects
Reduction of blood pressure usually occurs at the latest 60-90 minutes after oral intake of a single dose of captopril. The duration of effect is dose related. The reduction in blood pressure may be progressive, and several weeks of therapy may therefore be required in order to achieve the maximum therapeutic effect. The hypotensive effect of captopril and thiazide-type diuretics are additive.
Captopril causes a reduction in blood pressure in standing and supine positions in patients suffering from hypertension without causing a compensatory rise in heart rate, and without water or sodium retention.
Haemodynamic examinations revealed captopril to cause a significant reduction in peripheral arterial resistance. As a rule renal plasma flow and glomerular filtration rate remained clinically unchanged.
Blood pressure reduction occurred in most patients 15-30 minutes following oral administration of captopril while the maximum effect was achieved after 60-90 minutes. As a rule the maximum reduction in blood pressure of a defined dose of captopril could be observed after 3-4 weeks.
At the recommended daily dose, the antihypertensive effect is maintained during long-term therapy as well. Sudden discontinuation of captopril does not lead to a rapid excessive rise in blood pressure (rebound).
Treatment with captopril also causes a reduction in left ventricular hypertrophy.
Haemodynamic examinations conducted in patients suffering from heart failure demonstrated that captopril caused a reduction in peripheral systematic resistance as well as a rise in venous capacity. This caused a reduction in cardiac preload and afterload (decrease in ventricular filling pressure). Furthermore, an increase in cardiac output, stroke work index and exercise tolerance time was observed under treatment with captopril.

Clinical efficacy and safety
A large placebo-controlled study involving patients with left ventricular dysfunction (LVEF $\leq$ 40 %) after myocardial infarction, demonstrated that captopril (administered between the 3rd and 16th day after the infarction) prolonged the survival rate and reduced mortality related to cardiovascular dysfunction. The latter was manifested by delayed development of symptomatic heart failure as well as a decrease in necessary hospital admissions of patients suffering from heart failure compared to the placebo. In addition, captopril, in contrast to the placebo, also led to a reduction in reinfarction occurrence and/or cardiac revascularisation interventions and/or the need for additional medication such as diuretics and/or digitalis or an increase in dosage of such medication.
A retrospective analysis revealed that captopril reduced the occurrence of reinfarctions as well as the necessity for revascularisation interventions (neither principal criteria of study).
A further large placebo-controlled study involving patients suffering from myocardial infarction showed that captopril (administered within 24 hours after the infarction over a period of one month) significantly reduced overall mortality after 5 weeks in comparison to the placebo. The favourable effects of captopril on overall mortality were still detectable after one year. There was no evidence of adverse reactions with regard to early mortality on the first day of treatment.
The cardioprotective effect of captopril may be observed during the post-infarction period, regardless of patient's age or gender, area of infarction or concomitant treatment with a therapy that has been proven to be effective (thrombolytic substances, beta blockers and acetylsalicylic acid).

Two large randomized, controlled trials (ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trail) and VA NEPHRON-D (The Veterans Affairs

Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 mellitus and chronic kidney disease, cardiovascular disease, or both. The study terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Diabetic nephropathy in type I diabetics
A placebo-controlled, multicentric, double-blind clinical study revealed that captopril, compared to the placebo, significantly prolonged the interval (by 51 %) up to doubling of the initial creatinine concentration in insulin-dependent type I diabetics with proteinuria, both with and without hypertension (concomitant administration of other antihypertensive agents for blood pressure control allowed). Terminal renal failure (dialysis, transplantation) or death were significantly less frequent under treatment with captopril than with the placebo (51 %).
Captopril, administered over a period of over two years, reduced albumin excretion in patients with diabetes and microalbuminuria. In addition to the benefits associated with reduction of blood pressure under treatment with captopril, captopril also maintains renal function.

5.2 Pharmacokinetic properties

Absorption and distribution
Captopril is an orally effective substance that does not require biotransformation in order to be effective. Average minimal absorption is approx. 75 %. Peak plasma concentrations are reached within 60-90 minutes. The presence of food in the gastrointestinal tract reduces absorption by approx. 30-40 %. About 25-30 % of the circulating drug is bound to plasma proteins.
Animal experiments show that captopril does not pass the blood-brain barrier to any significant extent.

Biotransformation and elimination
The apparent elimination half-life of unchanged captopril in blood is approx. 2 hours. More than 95 % of the absorbed dosage is excreted in urine within 24 hours; 40-50 % as unchanged substance and the remainder as inactive disulfide metabolites (captopril sulfide and captopril cysteine sulfide).
Impaired renal function could lead to an accumulation of the substance. The dosage should therefore be reduced in patients with impaired renal function and/or the intervals between dosage should be prolonged (see section 4.2).

Lactation
In the report of twelve women taking oral captopril 100 mg 3 times daily, the average peak milk level was 4.7µg/L and occurred 3.8 hours after the dose. Based on these data, the maximum daily dosage that a nursing infant would receive is less than 0.002% of the maternal daily dosage.

5.3 Preclinical safety data

Animal studies conducted with captopril during organogenesis have not shown any teratogenic effect. However, captopril did lead to foetal toxicity in several species including foetal mortality towards the end of pregnancy, growth retardation and postnatal mortality in rats. Preclinical data based on conventional studies on safety pharmacology, chronic toxicity, genotoxicity and carcinogenicity show no further risk for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, anhydrous
Microcrystalline cellulose
Maize starch
Stearic acid
Colloidal anhydrous silica
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in dry place below 25 ºC. Protect from light.

6.5 Nature and contents of container

PVC/PVDC/aluminium blisters
Pack size: 20 or 100 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

33000.01.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

21.09.1995

10. DATE OF REVISION OF THE TEXT

04/2019

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription