SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Ena+HCT-Denk 20/12.5

2. Qualitative and quantitative composition

Active ingredients: Enalapril maleate and hydrochlorothiazide
One tablet contains 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide.
Other excipients: Lactose monohydrate
Please refer to item 6.1 for a complete list of other excipients.

3. Pharmaceutical form

White, round, tablets that are scored on one side, with lateral notches.
The score serves the sole purpose of breaking the tablet in order to make it easier to swallow and not to divide into two equal half-doses.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of essential hypertension.
Ena+HCT-Denk 20/12.5 as a fixed combination (20 mg enalapril / 12.5 mg hydrochlorothiazide) is indicated in those patients whose blood pressure is not adequately controlled with enalapril alone.

4.2 Posology, method and duration of administration

Individual dosage titration of the individual components is advised. If clinically justifiable, a direct switch from monotherapy to fixed combination therapy can be considered.

The recommended dose is 1 tablet *Ena+HCT-Denk 20/12.5* daily.

Patients with salt and/or volume depletion (e.g. vomiting, diarrhoea, concomitant diuretic treatment), heart failure or severe hypertension may experience excessive hypotension.

Patients with renal insufficiency
Ena+HCT-Denk 20/12.5 is not indicated in patients with severe renal insufficiency (creatinine clearance < 30 ml/min) (see section “Contraindications”).
The dosage should be carefully adjusted in patients with impaired renal function (creatinine clearance > 30 ml/min and < 80 ml/min) (gradual titration of the individual components).

Children and adolescents (under 18 years of age)
The combination of enalapril and hydrochlorothiazide is not recommended in children, as safety and efficacy in children has not been established.

Elderly patients
The dosage must be adjusted according to the renal function of the elderly patients (see section "Special warnings and precautions for use**"**).

Mode of application

Tablets do not have to be taken at mealtimes. The daily dose is to be taken in the morning with some fluids.

Duration of treatment

As long as there are no adverse drug reactions, treatment with these tablets is not limited to a certain period of time and can be continued according to clinical response. The attending physician will decide how long the treatment will take.

4.3 Contraindications

- Hypersensitivity to enalapril, other ACE inhibitors, hydrochlorothiazide or other thiazides, sulphonamides (look out for possible cross reactions) or to any of the other excipients;
- History of known angioedema associated with previous ACE inhibitor therapy and patients with hereditary or idiopathic angioedema;
- Severe renal failure (creatinine clearance < 30 ml/min) and conditions requiring renal dialysis;
- Severe hepatic failure (precoma/hepatic coma);
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6);

4.4 Special warnings and precautions for use

Enalapril

Symptomatic hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, hypotension is more likely to occur if the patient has been volume depleted, e.g. caused by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (please refer to section "Interaction" and section "Adverse drug reaction"). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is more likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high-dose loop diuretics, pre-existing hyponatraemia and decreased renal function. In these patients, therapy should be started under medical supervision and the patients should be monitored closely whenever the dose of enalapril and/or the diuretic is adjusted. Similar precautions may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or stroke.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which are normally tolerated without problems once the blood pressure has increased after volume expansion.

Aortic or mitral valve stenosis / hypertrophic cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal function impairment
In cases of renal function impairment (creatinine clearance < 80 ml/min), the initial dose of enalapril should be adapted in accordance with the creatinine clearance and then adjusted according to the clinical response. Routine monitoring of serum potassium and serum creatinine are part of normal medical practice for these patients.

Renal failure has been reported in association with enalapril, particularly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If renal failure associated with enalapril therapy is detected in good time and treated accordingly, it is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and serum creatinine when enalapril is given concomitantly with a diuretic. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. In a situation such as this, the possibility of an underlying renal artery stenosis should be considered (see section "Special warnings and precautions for use**"**)

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration and monitoring of renal function.

Kidney transplantation
There is no experience regarding the administration of *Ena+HCT-Denk 20/12.5* in patients with a recent kidney transplantation. Treatment with *Ena+HCT-Denk 20/12.5* tablets is therefore not recommended.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia / agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving treatment with ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia rarely occurs. Enalapril should be administered with the utmost caution to patients suffering from collagen disease, patients receiving immunosuppressant therapy, treatment with allopurinol or

procainamide or patients with a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed severe infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity / Angioneurotic oedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has rarely been reported in patients treated with ACE inhibitors, including enalapril. This may occur at any time during treatment. In such cases, enalapril should be discontinued promptly and appropriate monitoring and treatment should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

There have been very rare reports of fatalities due to angioneurotic oedema associated with oedema of the larynx or tongue. In patients where there is involvement of the tongue, glottis or larynx, one should anticipate a respiratory tract obstruction especially if they have had respiratory tract surgery in the past.
Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g. subcutaneous epinephrine solution 1:1000 (0.3 – 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Reports of angioedema associated with ACE inhibitor therapy have been more common in black people than in non-blacks.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see section “Contraindications”).

Anaphylactoid reactions during hymenoptera desensitisation
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

Anaphylactoid reactions during LDL apheresis
Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

Diabetic patients
In diabetics treated with oral antidiabetic agents or insulin, adjustment of blood glucose should be closely monitored during the first month of treatment with an ACE inhibitor.

Cough
Cough is a side effect associated with the use of ACE inhibitors. Characteristically, the cough is dry, non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery / anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril can block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin).
If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Lithium
The combination of lithium and enalapril is generally not recommended (see section "Interaction").

Ethnic differences
Like other ACE inhibitors, enalapril maleate is apparently less effective as an antihypertensive in black people than in non-blacks. This may be due to the fact that low plasma renin levels are more common in black hypertensive patients than other patients.

<u>Hydrochlorothiazide</u>

Renal function impairment
Thiazides may precipitate azotaemia in patients with renal disease. The effects of this active ingredient may be cumulative in patients with impaired renal function. If renal insufficiency persists (recognisable by the elevated non-protein nitrogen values), the

therapy needs to be checked carefully and discontinuation of the diuretic therapy should be considered.

Liver function impairment
In patients with impaired hepatic function or progressive liver disease, thiazide should only be administered with caution, as even minor changes in the fluid and electrolyte balance may precipitate hepatic coma.

Metabolism and endocrinal effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see section ”Interaction”). Latent diabetes may become manifest under thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout attack in certain patients.

Electrolyte disorders:
Like in all patients receiving diuretic therapy, serum electrolytes should be checked on a regular basis.
Thiazides (including hydrochlorothiazide) can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are xerostomia, thirst, weakness, lethargy, somnolence, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.
Although hypokalaemia may develop during the use of thiazide diuretics, concurrent therapy with enalapril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section “Interaction”).
Dilution hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does not usually require treatment.

Thiazide may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium without any known calcium metabolism disturbance. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Lupus erythematosus
Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Anti-doping test
Hydrochlorothiazide contained in this product can produce a positive analytic result in an anti-doping test.

Other precautions
In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy and bronchial asthma.

Combination enalapril / hydrochlorothiazide

Risk of hypokalaemia
Combining an angiotensin-converting inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Serum potassium levels should be checked regularly.

Combination with lithium
The combined use of *Ena+HCT-Denk 20/12.5* with lithium is not recommended due to the enhanced risk of lithium toxicity (see ”Interaction”).

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

Patients with the rare hereditary problems of galactose intolerance, lactase deficiency or glucose- galactose malabsorption should not take *Ena+HCT-Denk 20/12.5*.

4.5 Interaction with other medicaments and other forms of interaction

Enalapril

Potassium-sparing diuretics or potassium supplements
ACE inhibitors attenuate diuretic-induced potassium loss. Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium. Even if concomitant use is indicated because of demonstrated hypokalaemia, these agents should be used only with caution and with frequent monitoring of serum potassium (see section “Special warnings and precautions for use**”**).

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see section “Special warnings and precautions for use**”**). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

Other antihypertensive agents
Concomitant use of antihypertensive agents may increase the hypotensive effect of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section “Special warnings and precautions for use”).

Tricyclic antidepressants /antipsychotic agents / anaesthetics / narcotics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section “Special warnings and special precautions for use”).

Non-steroidal anti-inflammatory drugs (NSAIDs)
Chronic administration of NSAIDs may reduce the antihypertensive effect of ACE inhibitors.

NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effect of ACE inhibitors.

Antidiabetics:
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Alcohol
Alcohol enhances the hypotensive effect of ACE inhibitors.

Acetyl salicylic acid, thrombolytics and β blockers
Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β blockers.

<u>Hydrochlorothiazide</u>

Alcohol, barbiturates and narcotic analgesics
Potentiation of orthostatic hypotension may occur.

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulating laxatives
Hydrochlorothiazide can potentiate electrolyte imbalance, hypokalaemie in particular.

Antidiabetics (oral antidiabetics and insulin)
A dosage adjustment may be required (see section “Special warnings and precautions for use”).

Calcium salts and vitamin D
Concomitant use with thiazide diuretics may decrease calcium excretion resulting in increased serum calcium levels.

Cardiac glycosides
Increased risk of digitalis toxicity associated with thiazide-induced hypokalaemia.

Cholestyramine and colestipol:
These substances can delay or reduce absorption of hydrochlorothiazide.
Thiazuide diuretics are to be taken at least 1 hour prior to or 4 - 6 hours after this medication.

Pressor amines (e.g. adrenaline (epinephrine))
Possible decreased response to pressor amines but not sufficient to preclude their use.

Cytostatics (e.g. cyclophosphamide, fluorouracil, methotrexate):
Increased bone marrow toxicity (especially granulocytopenia) due to hydrochlorothiazide-induced reduction of renal excretion of cytostatic drugs.

Drug for gout (e. g. allopurinol, benzbromarone):
As hydrochlorothiazide may precipitate hyperuricaemia, the dosage of the gout medication may need to be raised.

Agents associated with torsades de pointes
Due to the risk of hypokalaemia, caution is advised during concomitant use of hydrochlorothiazide with agents associated with torsade de pointes, such as some antiarrhythmics, certain antipsychotics and other drugs which are known to precipitate torsade de pointes.

Non-depolarising (skeletal) muscle relaxants
Thiazide may increase the effect of tubocurarine.

Clinical chemical tests
Hydrochlorothiazide can falsify the diagnostic result of the bentiromide test. Thiazide can reduce the serum level of PBI (protein-bound iodine) without any signs of thyroid dysfunction.

<u>Combination enalapril / hydrochlorothiazide</u>
Potassium-sparing diuretics and potassium supplements
ACE inhibitors reduce diuretic-induced potassium loss. The use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium.
Even if concomitant use is indicated because of demonstrated hypokalaemia, these agents should be used with caution and with frequent monitoring of serum potassium (see section “Special warnings and precautions for use**”**).

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further enhance the already increased risk of lithium toxicity with

ACE inhibitors. Concomitant use of enalapril and hydrochlorothiazide with lithium is therefore not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

4.6 Pregnancy and lactation

Pregnancy

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

Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia 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 for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation
Enalapril:
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 Ena+HCT-Denk 20/12.5 in breastfeeding 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 Ena+HCT-Denk 20/12.5 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.

Hydrochlorthiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Ena+HCT-Denk 20/12.5 during breast feeding is not recommended. If Ena+HCT-Denk 20/12.5 is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Adverse drug reactions

The adverse drug reactions will be described in this section under the headings of the frequency of occurrence, as defined below:

Very common (≥1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1000)
Very rare (< 1/10,000); not known (cannot be assessed on the basis of the available data)

Enalapril

Blood and lymphatic system disorders
Uncommon: Anaemia (including aplastic and haemolytic).
Rare*:* Neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases.

Metabolism and nutrition disorders
Uncommon: Hypoglycaemia (see "Special warnings and special precautions for use, Diabetic patients").

Nervous system and psychiatric disorders
Common: Headache, depression.
Uncommon: Confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo.
Rare: Dream abnormality, sleep disorders.

Eye disorders
Very common: Blurred vision.

Cardiac and vascular disorders
Very common: Dizziness.
Common: Hypotension (including orthostatic hypotension), syncope, myocardial infarction or stroke, possibly secondary to excessive hypotension in high risk patients (see section "Special warnings and precautions for use"), chest pain, arrhythmia, angina pectoris, tachycardia.
Uncommon: Orthostatic hypotension, palpitations.

Rare: Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders
Very common: Cough.
Common: Dyspnoea.
Uncommon: Rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma.
Rare: Pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorder
Very common: Nausea.
Common: Diarrhoea, abdominal pain, taste alteration.
Uncommon: Ileus, pancreatitis, vomiting, dyspepsia, constipation, loss of appetite, gastric irritations, dry mouth, peptic ulcer.
Rare: Stomatitis/aphthous ulcerations, glossitis.
Very rare: Intestinal angioedema

Hepatobiliary disorders
Rare: Hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis including jaundice.

Skin and subcutaneous tissue disorders
Common: Rash, hypersensitivity/angioneurotic oedema: Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been described (see section "Special warnings and precautions for use**"**).
Uncommon: Diaphoresis, pruritus, urticaria, alopecia.
Rare: Erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma.

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders
Uncommon: Renal dysfunction, renal failure, proteinuria.
Rare: Oliguria.

Reproductive system and breast disorders
Uncommon: Impotence.
Rare: Gynaecomastia.

General disorders and administration site condition
Very common: Asthenia.
Common: Fatigue.
Uncommon: Muscle cramps, flushing, tinnitus, malaise, fever.

Investigations
Common: Hyperkalaemia, increase of serum creatinine.
Uncommon: Increases in blood urea, hyponatraemia.
Rare: Increases in liver enzymes and serum bilirubin.

Hydrochlorothiazide

Infections and parasitic diseases
Rare: Sialadenitis

Blood and lymphatic system disorders
Rare: Leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression

Metabolism and nutrition disorders
Very common: Hyperglycaemia, glucosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglyceride levels
Uncommon: Anorexia
Not known: Metabolic alkalosis

Psychiatric disorders:
Rare: Anxiety, depression, sleep disturbances

Nervous system disorders
Common: Light-headedness, headache
Uncommon: Loss of appetite
Rare: Paraesthesia

Eye disorders
Uncommon: Xanthopsia, transient blurred vision

Disorders of the ear and labyrinth
Not known: Vertigo

Heart disease
Common: Palpitations
Rare: Arrhythmia

Vascular disorders
Common: Orthostatic hypotension
Rare: Necrotic angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders
Common: Gastric irritations, diarrhoea, constipation, pancreatitis

Hepatobiliary disorders
Uncommon: Jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders
Uncommon: Photosensitivity reactions, rash, urticaria
Rare: Reactions resembling those of cutaneous lupus erythematosus, reactivation of

cutaneous lupus erythematosus, anaphylactic reactions, toxic epidermal necrolysis

Skeletal muscle, connective tissue and bone disorders
Rare: Muscle spasms

Renal and urinary disorders
Uncommon: Interstitial nephritis
Rare: Renal function impairment

General disorders
Common: Weakness.
Uncommon: Fever

Investigations
Common: Reversible increase in substances that are usually excreted in urine (creatinine, urea, uric acid).

4.9 Overdosage

Symptoms
Depending on the extent of the overdose, the following symptoms may occur: Persistent diuresis, electrolyte disturbances, severe hypotension, impaired consciousness (progressing to coma), convulsions, paresis, arrhythmia, bradycardia, circulatory shock, renal failure, paralytic ileus.

Treatment
If ingestion is recent, take measures aimed at preventing absorption (e.g. gastric lavage, administration of absorbents and sodium sulphate within 30 minutes of ingestion) and accelerating elimination. If hypotension occurs, the patient should be placed in the shock position and given an intravenous infusion of normal saline solution and volumen supply. If necessary, treatment with angiotensin II. If bradycardia or severe vagal reaction occur, administration of atropine. If necessary, pacemaker therapy. Water, electrolyte and acid-base balance and blood sugar should be monitored continuously. Potassium replacement is necessary for hypokalaemia. Enalaprilat may be removed from the blood stream by haemodialysis. The extent to which hydrochlorothiazide may be removed by haemodialysis is not known to date.

5. Pharmacological properties

Ena+HCT-Denk 20/12.5 is a combination of an angiotensin-converting enzyme inhibitor (enalapril) and a diuretic (hydrochlorothiazide).
Enalapril and hydrochlorothiazide are used alone and in combination in the treatment of hypertension. The hypotensive effects of both components are approximately additive. Enalapril can reduce the potassium loss associated with hydrochlorothiazide

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor, combination

ATC Code: C09BA02

Enalapril

Mode of action:
Enalapril maleate is the maleate salt of enalapril, a derivative of the two aminoacids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance, angiogensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. ACE inhibition causes a decrease in the angiotensin II plasma concentration; this in turn leads to increased plasma renin activity (due to removal of negative feedback on renin release) and decreased aldosterone secretion.

ACE is identical to kininase II. Thus enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril is antihypertensive even in patients with low-renin hypertension.

Enalapril has a hypotensive effect in hypertensive patients in a lying or standing position without causing any considerable rise in heart rate.

Pharmacodynamics
Effective suppression of ACE activity usually occurs 2 to 4 hours after oral administration of a single dose of enalapril. The antihypertensive effect normally begins 1 hour after ingestion while the maximum antihypertensive effect occurs 4 to 6 hours after ingestion. The duration of effect is dose-related. However, at the recommended doses the antihypertensive and haemodynamic effects have been shown to last at least 24 hours.

Hydrochlorothiazide

Mode of action:
Hydrochlorothiazide is a benzothiadiazine. Thiazides act directly on the kidneys by increasing both the sodium chloride and associated water excretion. Their clinically relevant principal area of attack is the early distal tubule. They inhibit the electroneutral Na-Cl co-transport in the luminal cell membrane. Potassium and magnesium are excreted in increased amounts, calcium in reduced amounts. Hydrochlorothiazide causes a slight excretion of hydrogen carbonate and chloride excretion exceeds sodium excretion. Metabolic alkalosis may develop under treatment with hydrochlorothiazide. Like other organic acids, hydrochlorothiazide is actively secreted in the proximal tubule. The diuretic effect is maintained in the case of metabolic acidosis or metabolic alkalosis. Altered sodium balance, reduction in extracellular water and plasma volume, altered renal vessel resistance as well as a reduced response to noradrenalin and angiotensin II are being discussed as possible mechanisms of the antihypertensive effect of hydrochlorothiazide.

Pharmacodynamics

The electrolyte and water excretion effect of hydrochlorothiazide takes effect after 2 hours, has a maximum effect after 3 - 6 hours, and lasts 6 - 12 hours. The antihypertensive effect occurs only after 3 – 4 days and can last for up to one week after the end of therapy.

Enalapril / hydrochlorothiazide
There are no studies to date regarding cardiovascular morbidity and mortality associated with enalapril and hydrochlorothiazide as a fixed combination. Epidemiological studies have shown that cardiovascular morbidity and mortality do recede under long-term treatment with hydrochlorothiazide.
The combination of enalapril maleate / hydrochlorothiazide has an antihypertensive and diuretic effect. Clinical studies have shown the antihypertensive effect of enalapril and hydrochlorothiazide to be synergistic.
The maximum antihypertensive effect occurred 2 to 6 hours after ingestion while the antihypertensive effect lasted over 24 hours.
Enalapril can reduce the potassium loss associated with hydrochlorothiazide.

5.2 Pharmacokinetic properties

Enalapril

Absorption
Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablets is approximately 60%. The absorption of oral enalapril is not affected by the presence of food in the gastrointestinal tract.

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur approximately 4 hours after an oral dose of enalapril tablets. The effective half-life for accumulation of enalaprilat in serum following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of treatment.

Distribution
At therapeutically relevant concentrations, no more than 60% of enalaprilat is bound to human plasma proteins.

Metabolism
Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

Elimination
Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril (approx. 20%).

Special patient populations
Exposure to enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40 - 60

ml/min) steady state AUC of enalaprilat was approximately twice as high as in patients with normal renal function after administration of 5 mg once daily. AUC was approximately eight times higher in patients with severe renal insufficiency (creatinine clearance ≤ 30 ml/min). The effective half-life of enalaprilat following multiple doses of enalapril is also prolonged at this level of renal insufficiency and time to steady state is delayed (see "Posology, method and duration of administration"). Enalaprilat can be removed from the general circulation by haemodialysis. Dialysis clearance is 62 ml/min.

Hydrochlorothiazide

Bioavailability
Approx. 80% of hydrochlorothiazide is absorbed from the gastrointestinal tract following oral administration. The systemic availability is 71 ± 15%.

Distribution
Plasma protein binding of hydrochlorothiazide is 65%; the relative distribution volume lies between 0.5 and 1.1 l/kg.

Metabolism and excretion
In healthy subjects, 95% of hydrochlorothiazide is excreted unchanged via the kidneys.

Elimination half-life
In subjects with normal renal function, the elimination half life is 2.5 hours. Maximum plasma levels (Tmax) are reached after 2 – 5 hours as a rule. Tmax is prolonged in subjects with impaired renal function and is approximately 20 hours in subjects with terminal renal insufficiency.

The diuretic effect occurs within 1 to 2 hours. The diuretic effect is dose-related and lasts between 10 and 12 hours while the antihypertensive effect is maintained for up to 24 hours.

Lactation:
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7µg/L (range 1.2 to 2.3 µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively breastfed infant would be about 0.16% of the maternal weight-adjusted dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2 µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10 mg in two mothers; enalapril levels were not determined.

5.3 Preclinical safety data

Based on conventional safety pharmacology studies and studies with regard to toxicity associated with multiple doses, genotoxicity and carcinogenic potential, preclinical data have revealed no particular risks for humans.

6. Pharmaceutical particulars

6.1 List of other excipients:

Sodium hydroxide, lactose monohydrate, pre-gelatinised starch, maize starch, magnesium stearate (herbal).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a dry place below 25 °C.
Protect from light.
Do not use after the expiry date.
Keep out of the reach and sight of children.

6.5 Nature and content of container

Blister packs (Al/OPA-Al-PVC) of 30 tablets.
Free medical samples containing 10 tablets.

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(s) in Germany

Not applicable.

9. Date of authorisation in Germany

Not applicable.

10. Date of information

06/2014

11. Prescription status

For medical prescription only.