SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Benazepril HCl/Hydrochloorthiazide 10/12,5, filmomhulde tabletten 10 mg/12,5 mg
Benazepril HCl/Hydrochloorthiazide 20/25, filmomhulde tabletten 20 mg/25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains benazepril hydrochloride 10 mg and hydrochlorothiazide 12.5 mg.
Excipient with known effect
Each film-coated tablet contains 106.9 mg lactose (as monohydrate).

Each film-coated tablet contains benazepril hydrochloride 20 mg and hydrochlorothiazide 25 mg.
Excipient with known effect
Each film-coated tablet contains 213.6 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
10/12.5 mg: round, pink, film-coated tablet, convex with a breaking notch on one side.
20/25 mg: white to off white, round film-coated tablet, convex with a cross breaking notch on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with essential hypertension who have insufficiently responded to treatment with benazepril as monotherapy.

4.2 Posology and method of administration

Posology

The administration of the fixed combination of benazepril and hydrochlorothiazide is usually recommended after dose titration with the individual components. When clinically appropriate a direct change from monotherapy to the fixed combination may be considered.
In patients who do not respond to monotherapy with benazepril (10 or 20 mg) once daily, therapy should be converted to half a tablet of Benazepril HCl/Hydrochlorothiazide 10/12.5. If the blood pressure cannot sufficiently be controlled after 3 to 4 weeks, a dose increase up to 10 mg benazepril HCl and 12.5 mg hydrochlorothiazide can be conducted. If the blood pressure is still not yet under control after the same period has passed, the dose increase can go up to 20 mg benazepril HCl and 25 mg hydrochlorothiazide.

In patients for whom this dosage scheme is not sufficient and in patients known to have severe hypertension or hypertension difficult to control, a dosage scheme of twice daily benazepril HCl/hydrochlorothiazide 20/25 mg should be considered. Concurrent administration of a second diuretic is not recommended.

Pretreatment with a diuretic
Patients already treated with hydrochlorothiazide or a thiazide diuretic without sufficient response to that may experience a further significant decrease in blood pressure through substitution with [Nationally completed name] 10/12.5. In these patients, treatment with the diuretic should be discontinued at least 3 days prior to treatment with Benazepril HCl/Hydrochlorothiazide 10/12.5. Patients treated with hydrochlorothiazide 25 or 50 mg once daily should be converted to [Nationally completed name] 10/12.5. The dosage should be then adjusted according to blood pressure response.

Substitution therapy
In patients already receiving benazepril and hydrochlorothiazide as separate tablets, Benazepril HCl/Hydrochlorothiazide 10/12.5 may be used to substitute these medicinal products. If the blood pressure is brought under control with the free combination, therapy should be converted to a dose of [Nationally completed name] 10/12.5 corresponding to the same quantity of benazepril.

Renal impairment and elderly
According to clinical studies, [Nationally completed name] is effective and well tolerated both in older and younger patients. The normal dose of [Nationally completed name] 10/12.5 is recommended in patients with creatinine clearance above 30 ml/min (serum creatinine approx. < 3 mg/dl or 265 µmol/l).

In elderly and in patients with mild renal dysfunctions (creatinine clearance 30-60 ml/min), the dosage should be determined with caution according to clinical response (see pharmacokinetic properties of hydrochlorothiazide). If diuretic therapy is necessary in patients with severe renal dysfunctions (creatinine clearance < 30 ml/min), combination of benazepril with a loop diuretic and not with a thiazide diuretic is recommended. [Nationally completed name] is therefore not recommended in patients with severe renal dysfunctions (see section 4.4).

Paediatric population

No data is available yet regarding administration of [Nationally completed name] in children and adolescents (< 18 years).

Method of administration
[Nationally completed name] should be taken at the same time everyday, preferably in the morning with one glass of water.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Known hypersensitivity to any other ACE inhibitor, to sulphonamides or thiazides (possible cross reactions)
- Anuria, severe renal (creatinine clearance < 30 ml/min) and hepatic failure
- Refractory hypokalaemia, hyponatriaemia and symptomatic hyperuricaemia
- History of angioedema with or without previous ACE inhibitor treatment.
- The concomitant use of [Nationally completed name] with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

- Concomitant use with sacubitril/valsartan therapy. [Nationally completed name] must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Warnings

Anaphylactoid and related reactions
Presumably because angiotensin converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including [Nationally completed name]) may experience a variety of undesirable effects, some of them serious.

Hypersensitivity/Angioedema
Angioedema of the face, lips, tongue, glottis and larynx has been reported in patients treated with ACE inhibitors including benazepril. In such cases, [Nationally completed name] should be immediately discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms. Where swelling is limited to the face and lips, the condition generally resolves either without treatment or with antihistamines. Angioedema with laryngeal oedema can be fatal. Where the tongue, glottis, or larynx are involved, appropriate therapy should be given immediately, e.g. subcutaneous adrenaline injection 1:1000 (0.3-0.5 mL) and/or measures to ensure a patent airway. The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black patients of African origin than in non-black patients.

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 [Nationally completed name]. Treatment with [Nationally completed name] 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.

Anaphylactoid reactions during desensitisation
Life-threatening anaphylactoid reactions were reported in two patients undergoing desensitising treatment with Hymenoptera venom (wasp-sting venom) while using ACE inhibitors. These reactions were avoided when ACE inhibitors were temporarily withheld.

Anaphylactoid reactions during membrane exposure
Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes while receiving an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Symptomatic hypotension
As with other ACE inhibitors, symptomatic hypotension has been observed in rare cases, typically in patients with volume or salt depletion as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. Volume and/or salt depletion should be corrected before starting therapy with [Nationally completed name].

[Nationally completed name] should be used cautiously in patients receiving concomitant therapy with other antihypertensives. The thiazide component of [Nationally completed name] may potentiate the action of other antihypertensive medicinal products. If hypotension occurs, the patient should be placed

in the supine position and if necessary given physiological sodium chloride solution intravenously (IV). Treatment with [Nationally completed name] can be continued once blood pressure and volume have returned to normal.

In patients with severe congestive heart failure ACE inhibitor therapy can cause excessive hypotension which may be associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure. In such patients, therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

Renal impairment
[Nationally completed name] should be used with caution in patients with renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated dosing may be cumulative. When the renin-angiotensin system is inhibited by benazepril, alterations in renal function may occur in susceptible patients. In patients with severe congestive heart failure, whose renal function may depend on the activity of the renin angiotensin system, treatment with ACE inhibitors (including benazepril) may lead to renal dysfunctions, oliguria and/or progressive azotaemia and (rarely) acute renal failure.

In a small study of hypertensive patients with renal artery stenosis in one or both kidneys, treatment with benazepril may lead to renal dysfunction, oliguria, increases in blood urea nitrogen and serum creatinine; these alterations were reversible on discontinuation or reduction in the dose of benazepril or diuretic therapy, or of both. If such patients are treated with [Nationally completed name], renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients receiving benazepril with no apparent pre-existing renal vascular disease have developed elevated blood urea nitrogen and serum creatinine levels (usually minor and transient), especially when benazepril was given with a diuretic.

Dose reduction or discontinuation of [Nationally completed name] may be required. It is necessary to monitor renal function when assessing hypertensive patients (see sections 4.3 and 4.2).

Agranulocytosis/neutropenia
Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression; such effects occur more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Not enough data are available from clinical trials of benazepril to show whether or not it causes a similar incidence of agranulocytosis.

Monitoring of the white blood cell count should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Hepatitis and hepatic failure
There have been rare reports of predominantly cholestatic hepatitis and isolated cases of acute liver failure, some of them fatal, in patients on ACE inhibitors. The mechanism is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevation of hepatic enzymes should discontinue the ACE inhibitor and be kept under medical surveillance.

Hepatic impairment
[Nationally completed name] should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor changes in fluid and electrolyte balance may precipitate hepatic coma (see “Hepatic failure”).

Systemic lupus erythematosus
Thiazide diuretics have been reported to exacerbate or activate systemic lupus erythematosus.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulphonamide or sulphonamide derivative medicinal products can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicinal product initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamides or penicillin allergy.

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute respiratory toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, [Nationally completed name] should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Precautions

Serum electrolyte changes

Serum potassium
Elevated serum potassium levels have been observed on rare occasions during treatment with ACE inhibitors, including benazepril. 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 co-trimoxazole 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).

Treatment with thiazide diuretics has been associated with hypokalaemia, hyponatraemia, and hypochloraemic alkaloid. These disturbances have sometimes caused one or more of the following symptoms: dry mouth, thirst, weakness, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and nausea, xerostomia, asthenia, somnolence, myospasms.

Hypokalaemia can also sensitise or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalaemia is greatest in patients suffering from cirrhosis of the liver, patients with rapid diuresis, patients whose oral electrolyte intake is inadequate, and patients receiving concomitant therapy with corticosteroids or ACTH. Monitoring of serum electrolytes should be performed initially and periodically with adequate intervals in order to detect any disturbance in serum electrolyte balance. Treatment with a potassium salt or potassium-sparing diuretic should be avoided in patients receiving an ACE inhibitor and thiazide diuretic, including [Nationally completed name], unless considered necessary (see section 4.5).

Calcium excretion is decreased by thiazides. Alterations of parathyroid gland function with hypercalcaemia and hypophosphataemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcaemia occurs, further diagnostic clarification is necessary. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Other metabolic disturbances
Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.
Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy; however at the 12.5 mg dose contained in [Nationally completed name], minimal or no effects were reported. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Cough
Persistent, non-productive cough has been reported with ACE inhibitors, presumably due to inhibited degradation of endogenous bradykinin. This cough always resolves after discontinuation of therapy. ACE inhibitor-induced cough must be considered in the differential diagnosis of cough.

Surgery/anaesthesia
Before surgery, the anaesthetist should be informed that the patient is receiving an ACE inhibitor. During anaesthesia with agents that induce hypotension, ACE inhibitors may block angiotensin II formation secondary to compensatory renin release. Hypotension occurring by this mechanism should be corrected by volume expansion.

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.

Aortic or mitral stenosis
As with all other vasodilators, including ACE inhibitors, special caution is indicated in patients suffering from aortic or mitral stenosis.

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).

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

4.5 Interactions with other medicinal products and other forms of interaction

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 benazepril. Potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when benazepril is co-administered with other agents that increase serum potassium, such as trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of benazepril with the above-mentioned medicinal products is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Other medicinal products affecting serum potassium level
The hypokalaemic effect of diuretics (including hydrochlorothiazide) may be increased by corticosteroids; ACTH, amphotericin, and carbenoxolone (see also sections 4.4 and 4.8).

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.

Lithium
Increased serum lithium levels and symptoms of lithium intoxication have been reported in patients receiving ACE inhibitors (including benazepril) during therapy with lithium.

Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity is presumably increased further when, as in therapy with [Nationally completed name] a thiazide diuretic is administered with the ACE inhibitor. Caution is called for if [Nationally completed name] and lithium are administered concomitantly, and frequent monitoring of serum lithium levels is recommended.

Antidiabetic agents
In rare cases, diabetic patients receiving an ACE inhibitor (including benazepril) concomitantly with insulin or oral antidiabetics may develop hypoglycaemia. It may be necessary to adjust the dose of insulin or oral antidiabetic when [Nationally completed name] is administered concomitantly. Such patients should therefore be advised about the possibility of hypoglycaemic reactions, and should be monitored accordingly.

Thiazide diuretics (including hydrochlorothiazide) may alter glucose tolerance. It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents.

Gold
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.

Other antihypertensive medicinal products
Thiazides potentiate the action of curare derivatives. Thiazides (including hydrochlorothiazide) potentiate the action of antihypertensive medicinal product (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium antagonists, ACE inhibitors).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ACE-inhibitors, angiotensin II receptor blockers or aliskiren
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).

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias (see also sections 4.4 and 4.8).

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid used as an anti-inflammatory medicinal product
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory medicinal products, attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Ion exchange resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

Bile acid-binding resins
Single doses of either cholestyramine or colestipol resins bind hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 % and 43 %, respectively.

Allopurinol and antineoplastic agents
Coadministration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, and may reduce the renal excretion of cytotoxic medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Amantadine and diazoxide
Coadministration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse events caused by amantadine, and may enhance the hyperglycaemic effect of diazoxide.

Anticholinergic agents
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach-emptying rate.

Calcium/vitamin D
Administration of thiazide diuretics with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Ciclosporin

Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Methyldopa
Haemolytic anaemia is reported in the literature if hydrochlorothiazide is concurrently used with methyldopa.

Carbamazepine
Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatremic reactions, and should be monitored accordingly.

Medicinal products 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. temsirolimus, sirolimus, everolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

4.6 Fertility, 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 2nd and 3rd trimester of pregnancy (see section 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 closely observed for hypotension (see also 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.

Breast-feeding

Benazepril:
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 [Nationally completed name] 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 [Nationally completed name] in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse event.

Hydrochlorothiazide:
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of [Nationally completed name] during breast-feeding is not recommended. If [Nationally completed name] is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

Since vertigo can occur with other antihypertensive medicinal products, especially with ACE inhibitors, it is advisable to exercise caution when driving or operating machines.

4.8 Undesirable effects

Adverse experiences occurring with benazepril/HCTZ were the same as those that have been reported with benazepril or hydrochlorothiazide, and were usually mild and transient. Adverse reactions reported with benazepril/HCTZ are listed below.

Very common	*≥1/10*
Common	*≥1/100 to <1/10*
Uncommon	*≥1/1,000 to <1/100*
Rare	*≥1/10,000 to <1/1,000*
Very rare	*<1/10,000*
Not known	*cannot be estimated from the available data*

Immune system disorders
Rare: angioedema, oedema of the lips and/or face (see section 4.4: anaphylactoid and related reactions).

Metabolism and nutrition disorders
Rare: hypokalaemia.
Very rare: hyponatraemia.

Psychiatric disorders
Rare: nervousness, anxiety.

Nervous system disorders
Common: headache, dizziness.
Rare: insomnia, vertigo, paraesthesias, somnolence.
Very rare: tinnitus.
Not known: syncope.

Cardiac disorders
Common: palpitations.
Rare: chest pain.

Vascular disorders
Common: orthostatic hypotension.
Rare: hypotension.

Respiratory, thoracic and mediastinal disorders
Common: cough, respiratory tract symptoms.

Gastrointestinal disorders
Common: abdominal discomfort.
Rare: diarrhoea, constipation, nausea, vomiting, abdominal pain.
Very rare: dysgeusia.

Skin and subcutaneous tissue disorders
Common: rash, flushing, pruritus, photosensitivity.

Musculoskeletal and connective tissue disorders
Rare: arthralgia, arthritis, myalgia, musculoskeletal pain.

Renal and urinary disorders
Common: pollakiuria.

General disorders and administration site conditions
Common: fatigue.

Investigations
Rare: increase in blood uric acid levels, blood urea increased, blood creatinine increased which were reversible on discontinuation of therapy. These changes are more likely to occur in patients with renal artery stenosis (see section 4.4).
Minor increases in blood urea nitrogen (BUN) and serum creatinine, which were reversible on discontinuation of therapy, were observed in patients receiving [Nationally completed name] 20/25 mg or higher doses (see section 4.4). A slight reduction in mean serum potassium was noted in some clinical studies, and only 0.2 % of the patients treated with [Nationally completed name] developed hypokalaemia (more than 0.5 mmol/l below the normal range). Hyponatraemia, elevated uric acid and decreased haemoglobin have also been reported in patients receiving [Nationally completed name].

Benazepril
With benazepril monotherapy and/or other ACE inhibitors more postmarketing experience is available and the following additional adverse reactions have been reported.

Blood and lymphatic system disorders
Very rare: thrombocytopenia (see section 4.4: Agranulocytosis, neutropenia), haemolytic anaemia.
Not known: agranulocytosis, neutropenia.

Immune system disorders
Not known: anaphylactoid reactions.

Metabolism and nutrition disorders
Not known: hyperkalaemia.

Cardiac disorder

Rare: angina pectoris, arrhythmia.
Very rare: myocardial infarction.

Gastrointestinal disorders
Very rare: pancreatitis.
Not known: small bowel angioedema.

Hepatobiliary disorders
Rare: hepatitis (predominantly cholestatic), cholestatic jaundice (see section 4.4: Hepatitis and hepatic failure).

Skin and subcutaneous tissue disorders
Rare: pemphigus.
Very rare: Stevens-Johnson syndrome.
Not known: psoriasis aggravation.

Renal and urinary disorders
Very rare: renal impairment.

Hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, sometimes in higher doses than those contained in [Nationally completed name].
The following adverse reactions have been reported in patients treated with thiazide diuretics alone (including hydrochlorothiazide).

Electrolytes and metabolic disorders
See section 4.4.

Others

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Not known: non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma). Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Blood and lymphatic system disorders
Rare: thrombocytopenia sometimes with purpura.
Very rare: leukopenia, agranulocytosis, bone marrow failure, haemolytic anaemia.
Not known: aplastic anaemia.

Immune system disorders
Very rare: hypersensitivity.

Metabolism and nutrition disorders
Common: decreased appetite.

Psychiatric disorders
Rare: Sleep disorder, depression.

Nervous system disorders
Rare: headache, dizziness, paraesthesia.

Eye disorders
Rare: Visual impairment, particularly in the first few weeks of treatment.
Not known: Choroidal effusion, acute myopia and secondary acute angle-closure glaucoma.

Cardiac disorders
Rare: arrhythmia.

Vascular disorders
Common: orthostatic hypotension which may be aggravated by alcohol, anaesthetics, or sedatives.
Very rare: necrotising vasculitis.

Respiratory, thoracic and mediastinal disorders
Very rare: respiratory distress including pneumonitis, and pulmonary oedema, acute respiratory distress syndrome (ARDS) (see section 4.4)

Gastrointestinal disorders
Common: mild nausea and vomiting.
Rare: abdominal discomfort, constipation, diarrhoea.
Very rare: pancreatitis.

Hepatobiliary disorders
Rare: cholestasis, jaundice.

Skin and subcutaneous tissue disorders
Common: urticaria and other forms of rash.
Rare: photosensitivity reactions.
Very rare: toxic epidermal necrolysis, cutaneous lupus-erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.
Not known: erythema multiforme.

Musculoskeletal and connective tissue disorders
Not known: muscle spasm.

Renal and urinary disorders
Uncommon: acute renal failure.
Not known: renal failure and impairment.

Reproductive system and breast disorders
Common: erectile dysfunction.

General disorders and administration site conditions
Not known: pyrexia, asthenia.

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 listed in Appendix V.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

4.9 Overdose

Symptoms
No specific information is available on the treatment of overdose with [Nationally completed name].

In poisoning due to an overdose of hydrochlorothiazide, the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Although there is limited experience of overdose with benazepril, the main sign to be expected is marked hypotension, which can be associated with electrolyte disturbances and renal failure.

Management
There is no specific antidote for either hydrochlorothiazide or benazepril. Treatment should be symptomatic and supportive. If ingestion is recent, induce vomiting or perform gastric lavage. Activated charcoal may be administered to reduce absorption. The patient's legs should be kept raised and lost fluids and electrolytes should be replaced. Monitor renal function until the patient's condition returns to normal.

Although the active metabolite benazeprilat is only slightly dialysable, dialysis might be considered to support normal elimination in overdosed patients with severely impaired renal function (see section 4.3). In the case of marked hypotension, give the appropriate therapy.

After intake of an overdose, admission into an intensive care unit is desirable in order to correct hypotension - which may be long-lasting - by means of intravenous administration of plasma-substituting agents or - if the result is insufficient - by catecholamines.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitor and diuretic, ATC code: C09B A07

[Nationally completed name] is a combination of an "angiotensin converting enzyme" inhibitor, benazepril, and a diuretic, hydrochlorothiazide. The antihypertensive effect of both components is synergistic.

After oral administration, benazepril hydrochloride is rapidly absorbed and then hydrolyzed to benazeprilat, an inhibitor of the angiotensin converting enzyme (ACE), which converts angiotensin I into angiotensin II. The consequences of this enzyme inhibition are:
- decrease in the production of angiotensin II;
- increase in the precursors angiotensin I and renin;
- hypotension, mainly due to peripheral vasodilation; vasodilation, decrease in the production of aldosterone associated with an increase in renal excretion of sodium ions and water and a decrease in renal excretion of potassium ions.

ACE is identical with kininase II.

As is the case with other ACE inhibitors, benazepril can inhibit the degradation of the vasodilator bradykinin by kininase; this inhibition may perhaps contribute to the antihypertensive effect.

Administration of benazepril to patients with hypertension results in a reduction in blood pressure both in supine and standing position with usually little or no orthostatic hypotension occurring thereby. After administration of one single oral dose, the antihypertensive effect sets in after approximately one hour; hypotension is at a maximum two to four hours after administration. The antihypertensive effect

lasts for at least 24 hours. During repeated administration, the maximum reduction in blood pressure is generally achieved after one week and continues during maintenance therapy. The antihypertensive effect is independent from race, age or basal plasma renin activity.

Abrupt discontinuation of administration of benazepril is not associated with a rapid increase in blood pressure.
In a study with healthy volunteers, single doses of benazepril resulted in an increase in renal perfusion without any effect on glomerular filtration rate.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the 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 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was 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.

Thiazide diuretics are effective especially in the distal part of the renal tubule via inhibition of NaCl re-absorption (via antagonism with regard to NaCl carriers). Increased quantity of Na^+ and water in the renal collecting tube and/or increased filtration rate lead to increased secretion and excretion of K^+ and H^+.
In addition, the absorption of Ca^{2+} is stimulated (due to an unknown mechanism).

In patients with normal renal function, diuresis is promoted already after administration of 12.5 mg hydrochlorothiazide. The resulting increase in urinary excretion of sodium and chloride and the relatively lover increase in potassium in urine are dose-dependent. The diuretic and natriuretic effect is apparent 1-2 hours after oral administration of hydrochlorothiazide, reaches its maximum after 4-6 hours and may continue for 10-12 hours.

Diuresis induced by thiazides initially leads to a decrease in plasma volume, cardiac output and systemic blood pressure. The renin angiotensin aldosterone system may be activated. The hypotensive effect is maintained with continued medication, probably due to the decrease in peripheral resistance; cardiac output returns to initial values, and the plasma volume remains somewhat lower.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a

possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

Benazepril, hydrochlorothiazide
Inhibition of the renin angiotensin system due to benazepril results in a synergistic antihypertensive effect with hydrochlorothiazide by counteracting the stimulating effect of hydrochlorothiazide. Stimulation of the renin angiotensin system leads to the fact that the blood pressure becomes more dependent on the angiotensin II-concentration, whereas the effectivity of benazepril is increased.

5.2 Pharmacokinetic properties

Absorption
There is no pharmacokinetic interaction between the components of [Nationally completed name] (benazepril HCL and hydrochlorothiazide), and the bioavailability of both components is not affected by concurrent administration. The combination tablets of [Nationally completed name] are bioequivalent to the administration of both components as single tablets.

At least 37 % of a dose of benazepril HCl administered orally is absorbed. The "prodrug" is then rapidly converted to the pharmacologically active metabolite benazeprilat. After administration on an empty stomach, the maximum plasma concentration of benazepril and benazeprilat is achieved after 0.5 and 1-1.5 hours, respectively. Hydrochlorothiazide is absorbed at 60-80 % after oral administration. Maximum plasma levels are reached within 1.5-3 hours after administration. Deviations in the absorption of benazepril HCl and hydrochlorothiazide as result of fasting are of minor clinical relevance.

In the therapeutic dose range, the systemic availability of benazepril, benazeprilat and hydrochlorothiazide is approximately directly proportional to the dose. Multiple administrations do not influence the pharmacokinetics of benazepril-HCl and hydrochlorothiazide.

Distribution
Benazepril and benazeprilat are bound to human serum proteins (especially albumin) at approx. 95 %. The distribution volume in steady state of benazeprilat is approximately 9 l.

Hydrochlorothiazide accumulates in erythrocytes. In the elimination phase, the concentration in erythrocytes is 3 to 9 times higher than in plasma. Approximately 40-70 % of hydrochlorothiazide is bound to plasma proteins. The distribution volume during the terminal elimination phase is estimated to be 3-6 l/kg (corresponding to 210-420 l with a bodyweight of 70 kg).

Biotransformation
Benazepril is metabolised to a large extent; the main metabolite is benazeprilat. Two other metabolites are acyl glucuronide conjugates of benazepril and benazeprilat. A very small part of hydrochlorothiazide is metabolised. The only found metabolite (in traces) is 2-amino-4-chloro-*m*-benzenedisulfonamide.

Elimination
Benazepril is completely eliminated from plasma after 4 hours, mainly via biotransformation. The elimination of benazepril is biphasic with an initial half-life of approximately 3 hours and a terminal half-life of approximately 22 hours. The terminal phase (from 24 hours) suggests a strong binding of benazepril to ACE. Benazeprilat is eliminated via kidney and bile; naturally, renal excretion is the main route in patients with normal renal function. Only 1 % of the dose is excreted in urine as unchanged benazepril; 20 % of the dose is excreted as benazeprilat.

The elimination of hydrochlorothiazide is biphasic with an initial half-life of approximately 2 hours and a terminal half-life (from 10 to 12 hours) of approximately 10 hours. Elimination takes place almost exclusively via the kidneys in patients with normal renal function. On average 50-75 % of an oral dose is recovered in urine in unchanged form.

Other special populations

Patients with congestive heart failure
Absorption of benazepril and conversion into benazeprilat are not affected. Since the elimination is somewhat slower, the trough concentration in steady state is higher in this group than in healthy individuals or hypertensive patients.

Elderly and patients with renal impairment
The pharmacokinetics of benazepril and benazeprilat are not significantly influenced by higher age or mild or moderate renal dysfunction (creatinine clearance 30-80 ml/min). The pharmacokinetics of hydrochlorothiazide is markedly influenced in these patients. The clearing of this diuretic is considerably reduced resulting in a substantial increase in the plasma concentration. Reduced clearing in elderly is attributable to impaired renal function. The effective dose in elderly and in patients with reduced renal function may then also be lower than in younger patients with normal renal function. [Nationally completed name] is contraindicated in patients with creatinine clearance of less than 30 ml/min.

Hepatic impairment
The kinetics of benazeprilat and hydrochlorothiazide are not influenced by hepatocirrhosis.

Lactation
In nine women given an oral dose of 20 mg of benazepril daily for 3 days (time postpartum not stated), peak milk levels of 0.9 μg/L of benazepril at 1 hour after the dose and 2 μg/L of its active metabolite benazeprilat at 1.5 hours after the dose were detected. It is estimated that the breastfed infant would receive a daily dose less than 0.14 % of the maternal weight-adjusted dose of benazepril.

5.3 Preclinical safety data

Preclinical data reveal no other specific hazard for human based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicity and carcinogenicity. No reproductive toxicity studies with the combination of benazepril and hydrochlorothiazide has been conducted. Animal studies conducted with benazepril or hydrochlorothiazide alone induced embryotoxic (benazepril) but no teratogenic effects in three species (benazepril, hydrochlorothiazide).
Other ACE inhibitors induced adverse events on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-agiotensin system and partly due to the ischemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.
In animal studies hydrochlorothiazide passes the placenta.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

tablet core:
Lactose monohydrate

Crospovidone
Hydrogenated castor oil
Cellulose, microcrystalline
Starch, pregelatinised (maize)
Silica colloidal anhydrous

film-coating material:
Lactose monohydrate
Hypromellose
Macrogol 4000
Titandioxide (E171)

Additional for [Nationally completed name] 10/12.5mg
Iron oxide, yellow (E 172)
Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The film-coated tablets are packed in Aclar-PVC/Aluminium blisters and inserted in a carton.

NL/H/0529/001-002:
Original packages containing 14, 28, 42, 50 and 98 tablets.

NL/H/0530/001-002:
Original packages containing 14, 28, 42, 50, 60 and 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORIZATION HOLDER

Hexal AG
Industriestrasse 25
D-83607 Holzkirchen
Duitsland

8. MARKETING AUTHORIZATION NUMBERS

RVG 28629 (Benazepril HCl/Hydrochloorthiazide 10/12,5, filmomhulde tabletten 10 mg/12,5 mg)
RVG 28630 (Benazepril HCl/Hydrochloorthiazide 20/25, filmomhulde tabletten 20 mg/25 mg)

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Datum van eerste verlenging van de vergunning: 22 december 2003
Datum van laatste hernieuwing: 18 november 2009

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8: 24 februari 2022