SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Enalaprilmaleaat/Hydrochloorthiazide 20/12,5, tabletten 20/12,5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide.

Excipient with known effect
Each tablet contains 85.1 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, oval, biconvex snap tap tablet, one side scored, other side marked “EH”

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension.

This fixed dose combination is indicated in patients whose blood pressure is not adequately controlled with enalapril alone.
This fixed dose may also replace the combination of 20 mg enalapril maleate and 12.5 mg hydrochlorothiazide in patients who have been stabilised on the individual active substances given in the same proportions as separate medicinal products.
This fixed dose combination is not suitable for initial therapy.

4.2 Posology and method of administration

Posology
The recommended dose is one tablet daily.

[nationally completed name] can be administered in a single dose/day with or without food.
Individual dose titration with both active substances can be recommended.
When clinically appropriate, direct change from ACE inhibitor monotherapy to the fixed combination may be considered.

Prior diuretic therapy
Treatment with diuretics should be discontinued 2 to 3 day before the start of the treatment with [Nationally completed name].

Renal impairment

- Creatinine clearance greater than 30 ml/min: The dose of enalapril should be titrated in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min before switching to the fixed combination. Loop diuretics are preferred to thiazides in this population. The dose of enalapril maleate and hydrochlorothiazide should be kept as low as possible (see section 4.4).
  Potassium and creatinine should be monitored periodically in these patients, e.g. every 2 months when the treatment has been stabilised (see section 4.4).
- Creatinine clearance < 30 ml/min: see section 4.3.

Special population
In salt/volume depleted patients, the starting dose is 5 mg enalapril or lower. Individual dose titration with enalapril and hydrochlorothiazide is recommended.

Elderly
The use in the elderly has been shown to be as good as in younger hypertensive patients. In case of physiological renal impairment, titration with the monocomponent enalapril is recommended prior to using the fixed combination.

Paediatric population
Safety and effectiveness of [nationally completed name] in children and adolescents has not been established.

Method of administration
Oral use.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Severe renal impairment (creatinine clearance ≤30 ml/min).
- Anuria.
- History of angioedema associated with previous ACE-inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Hypersensitivity to sulfonamide-derived medicinal products.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe hepatic impairment/hepatic encephalopathy.
- 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).
- 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

Enalapril maleate-Hydrochlorothiazide

Hypotension and electrolyte fluid imbalance
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving [nationally completed name], symptomatic hypotension is more likely to occur if the

patient has been volume - depleted, e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see sections 4.5 and 4.8). Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. Special attention should be paid to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. In hypertensive patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or renal dysfunction. In these patients, therapy must be started under medical supervision preferably in a hospital and the patients must be followed closely whenever the dose of enalapril and/or diuretic is adjusted.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
After volume repletion and establishment of satisfactory blood pressure, treatment can be reinstituted, either at a lower dose or either of the components may be used appropriately alone.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systematic blood pressure may occur with enalapril. This effect is anticipated and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

Renal impairment
[Nationally completed name] should not be administered to patients with renal insufficiency (creatinine clearance <80 ml/min and >30 ml/min) until titration of enalapril has shown the need for the dose present in this formulation (see section 4.2).

Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic (see section 4.4 Enalapril maleate, Renal impairment; Hydrochlorothiazide, Renal impairment). If this occurs, therapy with [nationally completed name] should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see section 4.4., Enalapril maleate, Renovascular hypertension).

Hyperkalaemia
The combination of enalapril and a low-dose diuretic cannot exclude the possibility of a hyperkalaemia to occur (see section 4.4, Enalapril maleate, Hyperkalaemia).
However, the combination of an ACE inhibitor and non-potassium-sparing diuretic does not preclude the development of hypokalaemia, in particular in diabetic or renally impaired patients. Plasma potassium must be regularly monitored.

Lithium
The combination of lithium with enalapril and diuretic agents is generally not recommended (see section 4.5).

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

Sodium
This medicinal products contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Enalapril maleate

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

Renal impairment
Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognized promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible (see sections 4.2 and 4.4, Enalapril maleate-Hydrochlorothiazide, Renal impairment; Hydrochlorothiazide, Renal impairment).

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 enalapril in patients with a recent kidney transplantation. Treatment with enalapril is therefore not recommended.

Haemodialysis patients
The use of enalapril is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients dialyzed 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.

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 (see section 4.4, Hydrochlorothiazide, Hepatic disease).

Neutropenia/Agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious 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.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. ACE inhibitors can cause hyperkalaemia 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, worsening of renal function, aged more than 70 years, diabetes mellitus, intercurrent events in particular dehydration, acute cardiac decompensation, metabolic acidosis and in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride) or those patients taking other medicinal products associated with increases in serum potassium (e.g., heparin, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers), hyperkalemia can occur. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. 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. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.4, Enalapril maleate-Hydrochlorothiazide, Hyperkalaemia; Hydrochlorothiazide, Metabolic and endocrine effects, and section 4.5).

Hypoglycaemia
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor should be told to closely monitor for hypoglycemia, especially during the first month of combined use (see section 4.4, Hydrochlorothiazide, Metabolic and endocrine effects, and section 4.5).

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including enalapril maleate. This may occur at any time during treatment. In such cases, [nationally completed name] should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips, the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. 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.

Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to Whites. However, in general it appears that Blacks have an increased risk for angioedema.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (Also see section 4.3).

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

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

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/anaesthesia
Enalapril blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or anaesthesia with agents that produce hypotension to compensate via the renin-angiotensin system. Hypotension which occurs due to this mechanism can be corrected by volume expansion (see section 4.5).

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

Pregnancy
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to 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).

Ethnic differences
As with other angiotensin converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Hydrochlorothiazide

Renal impairment
Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min. or below (i.e., moderate or severe renal insufficiency) (see section 4.2 and section 4.4, Enalapril maleate-Hydrochlorothiazide, Renal impairment; Enalapril maleate, Renal impairment). In the elderly, the value for creatinine clearance must be adjusted for age, weight and sex.
Hypovolaemia, secondary to diuretic-induced fluid and sodium loss at the beginning of treatment, leads to reduced glomerular filtration. This can cause an increase in blood urea and creatinine. This transient functional renal impairment is without consequence in patients with normal renal function, but can aggravate pre-existing renal impairment.
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotaemia. Cumulative effects of the medicinal product may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

Hepatic disease
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see section 4.4, Enalapril maleate, Hepatic failure). In this case, treatment with the diuretic must be stopped immediately.
[nationally completed name] is generally not recommended in combination with sultopride (see section 4.5).

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dose adjustment of antidiabetic agents including insulin, may be required (see section 4.4, Enalapril maleate, Hypoglycaemia).

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy; however, at the 12.5 mg dose of hydrochlorothiazide, minimal or no effect was reported. In addition, in clinical studies with 6 mg of hydrochlorothiazide no clinically significant effect on glucose, cholesterol, triglycerides, sodium, magnesium or potassium was reported.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. This effect on hyperuricaemia appears to be dose-related, and is not clinically significant at the 6 mg dose of hydrochlorothiazide. In addition, enalapril may increase urinary uric acid and thus attenuate the hyperuricaemic effect of hydrochlorothiazide.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

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 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 4.5).

Hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and does usually not require treatment.

Natraemia
Sodium levels must be assessed before the initiation of treatment, and at regular intervals thereafter. All diuretic treatment can cause hyponatraemia, with potentially serious consequences. Since a decrease in natraemia may initially be asymptomatic, regular monitoring is essential and must be even more frequent in at-risk populations such as the elderly, malnourished and cirrhotic (see sections 4.8 and 4.9).

Kalaemia
Potassium depletion and hypokalaemia are the major risks associated with thiazide and related diuretics. Hypokalaemia (< 3.5 mmol/l) must be prevented in certain at-risk populations, such as elderly and/or malnourished patients, especially when receiving combination therapy, cirrhotic patients with oedema and ascites, coronary patients, patients with heart failure. In these cases, hypokalaemia increases the cardiotoxicity of digitalis glycosides and the risk of arrhythmia.
In patients with a long QT interval, whether congenital or substance-induced, hypokalaemia increases the risk of severe arrhythmia, in particular potentially fatal torsade de pointes, especially in patients with bradycardia.
Potassium levels must be regularly monitored, starting in the first week of treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of latent hyperparathyroidism. Thiazides should be discontinued before testing parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

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

Hypersensitivity
In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

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 sulfonamides 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.

4.5 Interaction with other medicinal products and other forms of interaction

Enalapril maleate-Hydrochlorothiazide

Other antihypertensive agents
Concomitant use of these agents may increase the hypotensive effects of enalapril and hydrochlorothiazide. 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 [nationally completed name] with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 (COX-2) inhibitors
Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 (COX-2) inhibitors may reduce the effect of diuretics and other antihypertensive medicinal products. Therefore, the antihypertensive effect of angiotensin II receptor antagonists, ACE inhibitors or diuretics may be attenuated by NSAIDs including selective COX-2 inhibitors.

The co-administration of NSAIDs (including COX-2 inhibitors) and angiotensin II receptor antagonists or 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 patients who are volume-depleted, including those on diuretic therapy).

Enalapril maleate

Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes
ACE inhibitors attenuate diuretic induced potassium loss. Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with enalapril. Potassium-sparing diuretics (e.g., eplerenone, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when enalapril 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 enalapril with the above-mentioned medicinal products is not recommended. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see section 4.4).

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.

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).

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 sections 4.2 and 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

Tricyclic antidepressants/Antipsychotics/Anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (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 (see sections 4.4 and 4.8).

Alcohol
Alcohol enhances the hypotensive effect of ACE inhibitors.

Acetylsalicylic acid, thrombolytics and β-blockers
Enalapril can be safely administered concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics and β-blockers.

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 including enalapril.

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

Hydrochlorothiazide

Non-depolarising muscle relaxants
Thiazides may increase the responsiveness to tubocurarine.

Alcohol, barbiturates, antidepressants or opioid analgesics
Potentiation of orthostatic hypotension may occur.

Antidiabetic medicinal products (oral agents and insulin)
The treatment with a thiazide may influence the glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be required (see sections 4.4 and 4.8). Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Cholestyramine and colestipol resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when enalapril/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):
Class Ia antiarrythmics (e.g., quinidine, hydroquinidine, disopyramide, procainamide).
Class III antiarrythmics (e.g., amiodarone, sotalol, dofetilide, ibutilide).
Some antipsychotics (e.g., thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
Others (e.g., bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Digitalis glycosides

Hypokalaemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalaemia.

Kaliuretic diuretics (e.g., furosemide), carbenoxolone, or laxative abuse
Hydrochlorothiazide may increase the loss of potassium and/or magnesium.

Pressor amines (e.g., noradrenaline)
The effect of pressor amines may be decreased but not sufficient to preclude their use.

Cytostatics (e.g., cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Other antihypertensive medicinal products
Additive effect.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dose adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dose of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g., atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Salicylates
In case of high doses of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa
There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

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

Calcium salts and vitamin D
Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dose should be adjusted accordingly.

Laboratory test interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine
Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine contrast media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product.
Patients should be rehydrated before the administration.

Amphotericin B (parenteral)
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

Paediatric population
Interaction studies have only been performed in adults.

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 contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
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 inhibitors 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 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

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 [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

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur (see section 4.8).

4.8 Undesirable effects

Enalapril/hydrochlorothiazide is usually well-tolerated. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy.

The most common side effects reported during clinical study with enalapril/hydrochlorothiazide were headache and cough.

The following undesirable effects have been reported for enalapril/hydrochlorothiazide, enalapril alone or hydrochlorothiazide alone either during clinical studies or after the medicinal product was marketed include:

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

Table 1: Undesirable effects with enalapril maleate/hydrochlorothiazide

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations			Sialadenitis			

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)						Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Blood and lymphatic system disorders			Anaemia (including aplastic and haemolytic)	Neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow suppression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases		
Immune system disorders				Anaphylactic reaction		
Endocrine disorders						Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders		Hypokalaemia, increase of cholesterol, increase of triglycerides, hyperuricaemia	Hypoglycaemia (see section 4.4), hypomagnesaemia, gout*, electrolyte balance disorders, including hyponatraemia	Increase in blood glucose	Hypercalcaemia (see section 4.4)	

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Nervous system and psychiatric disorders		Headache, syncope, taste alteration, depression	Confusion, somnolence, insomnia, nervousness, paresthesia, vertigo decreased libido*, restlessness	Dream abnormality, sleep disorders, paresis (due to hypokalaemia)		
Eye disorders	Blurred vision		Transient accommodation disorders, xanthopsia			
Ear and labyrinth disorders			Tinnitus			
Cardiac and vascular disorders	Dizziness	Hypotension, orthostatic hypotension, rhythm disturbances, angina pectoris, tachycardia	Flushing, palpitations, necrotising vasculitis, myocardial infarction or cerebrovascular accident[&], possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Raynaud's phenomenon		
Respiratory, thoracic, and mediastinal disorders	Cough	Dyspnoea	Rhinorrhoea, sore throat and hoarseness, bronchospasm /asthma	Pulmonary infiltrates, respiratory distress (including pneumonitis and pulmonary oedema), rhinitis, allergic alveolitis/eosinophilic pneumonia		

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Gastrointestinal disorders	Nausea	Diarrhoea, abdominal pain	Ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer, flatulence*	Stomatitis/aphthous ulcerations, glossitis	Intestinal angioedema	
Hepatobiliary disorders				Hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)		

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Skin and subcutaneous tissue disorders		Rash (exanthema) hypersensitivity/angioedema: angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4)	Diaphoresis, pruritus, urticaria, alopecia, photosensitization	Erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus		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 leucocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.
Musculoskeletal, connective tissue, and bone disorders		Muscle cramps†	Arthralgia*			
Renal and urinary disorders			Renal dysfunction, renal failure, proteinuria	Oliguria, interstitial nephritis		
Reproductive system and breast disorders			Impotence	Gynaecomastia		

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
General disorders and administration site conditions	Asthenia	Chest pain, fatigue	Malaise, fever			
Investigations		Hyperkalaemia, increases in serum creatinine	Increases in blood urea, hyponatraemia	Elevations of liver enzymes, elevations of serum bilirubin		

[&]Incidence rates were comparable to those in the placebo and active control groups in the clinical trials.
*Only seen with doses of hydrochlorothiazide 12.5 mg and 25 mg.
† The frequency of muscle cramps as common pertains to doses of hydrochlorothiazide 12.5 mg and 25 mg, whereas, the frequency of the event is uncommon as it pertains to 6 mg doses of hydrochlorothiazide.

Description of selected adverse reactions
Non-melanoma skin cancer: 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).

Related to hydrochlorothiazide
Adverse reactions not mentioned above

Metabolism and nutrition disorders:
Not known: glycosuria

Nervous system disorders:
Not known: decreased appetite, light-headedness

Eye disorders:
Not known: choroidal effusion, acute myopia, acute angle-closure glaucoma

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

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*.

4.9 Overdose

No specific information is available on the treatment of overdose with [nationally completed name]. Symptoms of overdose are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure. Treatment is symptomatic and supportive. Therapy with [nationally completed name] should be discontinued and the patient observed closely. Suggested measures include induction of emesis, administration of activated charcoal, and administration of a laxative if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalapril maleate
The most prominent features of overdose reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdose of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril maleate, respectively.

The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by hemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis.

In addition to the expected diuresis, overdose of thiazides may produce varying degrees of lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function, and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown.
Gastrointestinal irritation as well as an increase of blood urea nitrogen (BUN) were reported, and especially in patients with impaired renal function it can come changes of the serum electrolytes.

Clinically, nausea, vomiting, hypotension, cramps, dizziness, somnolence, confusional states, polyuria or oliguria to the point of anuria (through hypovolaemia) may occur.

If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: enalapril and diuretics
ATC code: C09B A02

Mechanism of action

ASSOCIATED WITH ENALAPRIL
Enalapril maleate is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma

angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of 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.

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.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE
Hydrochlorothiazide is a thiazide diuretic which acts as fluid-expelling and blood pressure-lowering agent by inhibition of substances which increase the tubular re-absorption of sodium in the cortical diluting segment.
It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

Characteristics of the antihypertensive therapy

Enalapril
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.
Administration of enalapril to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.
Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril has not been associated with rapid increase in blood pressure.
Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.
In short-term clinical studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.
When given together with thiazide-type diuretics, the blood pressure-lowering effects of enalapril are at least additive. Enalapril may reduce or prevent the development of thiazide-induced hypokalaemia.

Hydrochlorothiazide
The time to onset of diuretic activity is approximately 2 hours. Diuretic activity reaches a peak after 4 hours and is maintained for 6 to 12 hours.
Above a certain dose, thiazide diuretics reach a plateau in terms of therapeutic effect whereas adverse reactions continue to multiply. When treatment is ineffective, increasing the dose beyond recommended doses serves no useful purpose and often gives rise to adverse reactions.

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).

ASSOCIATED WITH THE COMBINATION
In clinical studies, the concomitant administration of enalapril and hydrochlorothiazide reduced blood pressure more significantly than either substance alone.
The administration of enalapril inhibits the renin-angiotensin-aldosterone system and tends to reduce the hydrochlorothiazide-induced potassium.
Combination of an ACE inhibitor with a thiazide diuretic produces a synergistic effect and also lessens the risk of hypokalaemia provoked by the diuretic alone.

5.2 Pharmacokinetic properties

Co-administration of enalapril and hydrochlorothiazide in various doses has little or no effect on the bioavailability of these two substances.

ASSOCIATED WITH ENALAPRIL

Absorption
Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within 1 hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. The absorption of oral enalapril is not influenced by the presence of food in the gastrointestinal tract.

Distribution
Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent ACE inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. The effective half-life for accumulation of enalapril following concentrations of enalaprilat were reached after four days of treatment.
Over the range of concentrations which are therapeutically relevant, enalapril binding to human plasma proteins does not exceed 60%.

Lactation
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7 µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7 µg/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 breast-fed infant would be about 0.16% of the maternal weight-adjusted dose. 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 1.44 µg/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.

Biotransformation
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 (about 20%).

Renal impairment
The exposure of 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 two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 ml/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed (see section 4.2 ‘Renal impairment’).
Enalaprilat may be removed from the general circulation by haemodialysis. The dialysis clearance is 62 ml/min.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Absorption
Oral absorption of hydrochlorothiazide is relatively rapid.
The bioavailability of hydrochlorothiazide varies between 60 and 80%. The time to peak plasma concentration (t_{max}) varies between 1.5 and 5 hours, with a mean of about 4 hours.

Distribution
Protein binding is approximately 40%.
The mean plasma half-life in fasted individuals has been reported to be 5 to 15 hours.

Elimination
Hydrochlorothiazide is eliminated rapidly by the kidney and excreted unchanged (> 95%) in the urine. At least 61% of the oral dose is eliminated unchanged within 24 hours.

In renal and cardiac impairment, as in the elderly, the renal clearance of hydrochlorothiazide is reduced, and the elimination half-life increased. Elderly subjects also show increased peak plasma concentrations.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation.
The compound has been shown to cross the placenta and is secreted in milk.
Angiotensin converting enzyme inhibitors, as a class, have been shown to be foetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester.
Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, dihydrate
Lactose monohydrate
Magnesium stearate
Maize starch
Sodium hydrogen carbonate
Talc

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

3 years.

6.4. Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5. Nature and contents of container

The tablets are packed in OPA-Al-PVC/Al blisters which are inserted into a carton folder.
Pack sizes: 10, 14, 20, 28, 30, 49, 50, 50x1, 60, 84, 90, 98, 100 tablets
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Hexal AG
Industriestrasse 25
D-83607 Holzkirchen
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 34510

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 30 oktober 2006.
Datum van laatste verlenging: 22 april 2010.

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8 ; 8 april 2022