SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Enalapril maleate/Hydrochlorothiazide 20 mg/12.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: Also contains 130.10 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pale yellow colour, circular, biconvex uncoated tablets with breakline on one side and plain on the other side.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Enalapril maleate / Hydrochlorothiazide Tablets are indicated for the treatment of mild to moderate hypertension in patients who have been stabilised on the individual components given in the same proportions. (See sections 4.3, 4.4, 4.5 and 5.1.)

4.2 Posology and method of administration

Posology

The dosage of this medicine should be determined primarily by the experience with the enalapril maleate component.

Adults:

Essential hypertension

The usual dosage is one tablet, taken once daily. If necessary, the dosage may be increased to two tablets, taken once daily.

Prior diuretic therapy: symptomatic hypotension may occur following the initial dose of this medicine; this is more likely in patients who are volume and/or salt depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with this medicine.

Dosage in renal insufficiency
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).

In patients with creatinine clearance of >30 mL/min and <80 mL/min this medicine should be used only after titration of the individual components.

Elderly
In clinical studies the efficacy and tolerability of enalapril maleate and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

Paediatric population
Safety and effectiveness in children have not been established.

Method of administration:

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance(s)or to any of the excipients listed in section 6.1
- Severe renal impairment (creatinine clearance ≤ 30 mL/min)
- Anuria
- History of angioneurotic oedema associated with previous ACE-inhibitor therapy
- Hereditary or idiopathic angioedema
- Hypersensitivity to sulfonamide-derived drugs
- Second and third trimesters of pregnancy (see section 4.4 and 4.6)
- Severe hepatic impairment
- Stenosis of the renal arteries
- The concomitant use of Enalapril maleate/Hydrochlorothiazide 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).
- Combination with sacubitril/valsartan due to the increased risk of angioedema. Do not administer this medicine within 36 hours of switching

to or from sacubitril/valsartan, a product containing a neprilysin inhibitor. (see 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 this medicine, symptomatic hypotension is more likely to occur if the patient has been volume depleted, e.g., by diuretic therapy, dietary salt restriction, 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 ischemic 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, hyponatraemia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of this medicine and/or diuretic is adjusted. Similar considerations may apply 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.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with this medicine. 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 this medicine may be necessary.

Renal Function 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 recognised promptly and treated

appropriately, renal failure when associated with therapy with enalapril is usually reversible.

This medicine 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 Special warnings and precautions for use, Enalapril Maleate, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4). If this occurs, therapy with this medicine should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see Special warnings and precautions for use, Enalapril Maleate, Renovascular Hypertension in section 4.4)

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.

Hyperkalaemia
The combination of enalapril and a low-dose diuretic cannot exclude the possibility of a hyperkalaemia to occur (see Special warnings and precautions for use, Enalapril Maleate, Hyperkalaemia in section 4.4).

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

Important information regarding the ingredients of this medicine

Lactose

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

Paediatric population

Safety and efficacy in children has not been established.

Enalapril Maleate

Aortic Stenosis/Hypertrophic Cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal Function Impairment
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 section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4).

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.

Haemodialysis Patients
The use of enalapril is not indicated in patients requiring dialysis for renal failure. Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Kidney Transplantation
There is no experience regarding the administration of enalapril in patients with recent kidney transplantation. Treatment with enalapril is therefore not recommended.

Hepatic failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see Special warnings and precautions for use, Hydrochlorothiazide, Hepatic Disease in section 4.4).

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. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, inter-current events in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g., heparin, trimethoprim-containing products such as cotrimoxazole). The use of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other drugs that may increase serum potassium, particularly in patients with impaired renal function may lead to a significant increase in serum potassium.

Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. 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 Special warnings and precautions for use, Enalapril

maleate-Hydrochlorothiazide, Hyperkalemia; Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 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 hypoglycaemia, especially during the first month of combined use (see Special warnings and precautions for use, Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 and section 4.5).

Hypersensitivity/ Angioneurotic Oedema
Angioneurotic oedema 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, this medicine should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

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. (see section 4.3).

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.

The combination of enalapril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of enalapril therapy. If treatment with sacubitril/valsartan is stopped, enalapril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5)

Anaphylactoid Reactions during Hymenoptera Desensitisation

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

Anaphylactoid Reactions during LDL-Apheresis

Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening 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 non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

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).

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 Function 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 Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Enalapril Maleate, Renal Function Impairment in section 4.4).

This medicine should not be administered to patients with renal insufficiency (creatinine clearance ≤80 mL/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

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 Special warnings and precautions for use, Enalapril Maleate, Hepatic Failure in section 4.4).

Metabolic and Endocrine Effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see Special warnings and precautions for use, Enalapril Maleate, Diabetic patients in section 4.4). Thiazides may decrease serum sodium, magnesium and potassium levels.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy; however, at the 12.5 mg dose of hydrochlorothiazide contained in enalapril maleate / hydrochlorothiazide tablets, 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.

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.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. This effect on hyperuricemia appears to be dose-related. In addition

enalapril may increase urinary uric acid and thus may 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 hypochloremic 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 not usually require treatment.

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

Anti-doping test

Hydrochlorothiazide contained in this 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 and bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

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).

Eye disorders
Choroidal effusion, acute myopia and secondary angle-closure glaucoma: Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

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, Enalapril maleate / Hydrochlorothiazide 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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
Clinical trial data have 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).

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 this medicine 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 (NSAIDs) including selective cyclooxygenase-2 (COX-2) inhibitors
Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. 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). Therefore, the combination should be administered with caution in patients with compromised renal function.

Enalapril Maleate

Potassium-sparing Diuretics or Potassium Supplements, or other drugs that may increase serum potassium

ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g., spironolactone, eplerenone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes or other drugs that may increases serum potassium (e.g., heparin, trimethoprim-containing products such as cotrimoxazole) may lead to significant increases in serum potassium. 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).

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.

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).

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.

Mammalian Target of Rapamycin (mTOR) inhibitors

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).

Neprilysin Inhibitors

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.4).

Medicines increasing the risk of angioedema

The concomitant use of enalapril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema.
Sacubitril/valsartan must not be started until 36 hours after taking the last dose of enalapril therapy. Enalapril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors (see section 4.5).

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment (see sections 4.4 and 4.8).

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

Hydrochlorothiazide

Non-depolarising Muscle Relaxants
Thiazides may increase the responsiveness to tubocurarine.

Alcohol, Barbiturates, or Opioid Analgesics
Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (Oral Agents and Insulin)
Dosage adjustment of the antidiabetic drug may be required (see sections 4.4 and 4.8).

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 gastro-intestinal tract by up to 85 and 43 percent, respectively.

Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)
Increased risk of torsades de pointes.

Digitalis Glycosides
Hypokalaemia can sensitise 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 (see section 4.5).

Cytostatics (e.g., Cyclophosphamide, Methotrexate)
Thiazides may reduce the renal excretion of cytotoxic drugs and potentiate their myelosuppressive effects.

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 second and third trimester of pregnancy (see sections 4.3 and 4.4).

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

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

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). Maternal oligohydramnios, presumably representing decreased foetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development.

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 this medicine 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 this medicine in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

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 this medicine during breast feeding is not recommended. If these tablets are 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

Summary of the safety profile

Enalapril maleate / Hydrochlorothiazide Tablets are 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 maleate / Hydrochlorothiazide Tablets were headache and cough.

The following undesirable side effects have been reported for enalapril alone or hydrochlorothiazide alone either during clinical studies or after the drug was marketed.

Tabulated list of adverse reactions

Table 1. Undesirable effects of Enalapril maleate / Hydrochlorothiazide Tablets

System organ class	**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)**
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 depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases		
Endocrine						Syndrome of

disorders						inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders		Hypokalaemia, increase of cholesterol, increase of triglycerides, hyperuricaemia	Hypoglycaemia (see section 4.4)), hypomagnesaemia, gout**	Increase in blood glucose	Hypercalcaemia (see section 4.4)	
Nervous system and psychiatric disorders		Headache, depression, syncope, taste alteration	Confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, decreased libido**	Dream abnormality, sleep disorders, paresis (due to hypokalaemia)		
Eye disorders	Blurred vision					Choroidal effusion
Ear and labyrinth disorders			Tinnitus			
Cardiac and vascular disorders	Dizziness	Hypotension, orthostatic hypotension, rhythm disturbances, angina pectoris, tachycardia	Flushing, palpitations, 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, bronchospas	Pulmonary infiltrates, respiratory distress (including pneumonitis and	Acute respiratory distress syndrome (ARDS) (see	

			m/asthma	pulmonary oedema), rhinitis, allergic alveolitis/ eosinophilic pneumonia	section 4.4)	
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)		
Skin and subcutaneous tissue disorders		Rash (exanthema) hypersensitivity/ angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4)	Diaphoresis, pruritus, urticaria, alopecia	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. Psoriasis and psoriasiform dermatitis.
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	Gynecomastia		
General disorders and administration site conditions	Asthenia	Chest pain, fatigue	Malaise, fever			
Investigations		Hyperkalaemia, increases in serum creatinine	Increases in blood urea, hyponatremia	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).

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No specific information is available on the treatment of overdosage with this medicine. Treatment is symptomatic and supportive. Therapy with this medicine 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
Symptoms
The most prominent features of overdosage 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 overdosage 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.

Management
The recommended treatment of overdosage is intravenous infusion of normal saline 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 sulfate). Enalaprilat may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

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

Management
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: C09 BA02.

Enalapril maleate

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, which leads to increased plasma renin activity (due to removal of negative feedback on renin release), and decreased aldosterone secretion.

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

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

Enalapril maleate - hydrochlorothiazide
Hydrochlorothiazide is a diuretic and antihypertensive agent which increases plasma renin activity. Although enalapril alone is antihypertensive even in

patients with low-renin hypertension, concomitant administration of hydrochlorothiazide in these patients leads to greater reduction of blood pressure.

Dual Blockade

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), 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.

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 (≥50,000mg 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).

5.2 Pharmacokinetic properties

Absorption

Oral enalapril maleate is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril maleate is approximately 60%. Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. Except for conversion to enalaprilat, there is no evidence of significant metabolism of enalapril. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding to ACE. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril maleate. The absorption of oral enalapril maleate is not influenced by the presence of food in the gastro-intestinal tract. The extent of absorption and hydrolysis of enalapril are similar for the various doses in the recommended therapeutic range.

Distribution

Studies in dogs indicate that enalapril crosses the blood-brain barrier poorly, if at all; enalaprilat does not enter the brain. Enalapril crosses the placental barrier. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Biotransformation

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney.

Elimination

Excretion of enalapril is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of

oral enalapril maleate is 11 hours. When plasma levels of hydrochlorothiazide have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

Renal impairment
Enalaprilat may be removed from the general circulation by haemodialysis.

Lactation
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7μg/L (range 0.54 to 5.9 μg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7μg/L (range 1.2 to 2.3μg/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 dosage. A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 μg/L 4 hours after a dose and peak enalaprilat levels of 0.75 μg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 hour period was 1.44μg/L and 0.63 μg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2μg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.

5.3 Preclinical safety data
No relevant information.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate

Maleic acid

Pregelatinised starch

Maize starch

Yellow ferric oxide E172

Sodium stearyl fumarate

6.2 Incompatibilities
Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Aluminium / Aluminium blister packs of tablets inserted into a carton package

Pack size(s): 10, 28, 30, 50, 56 and 98 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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