

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Enalapril /Hydrochlorothiazide 20 mg/12.5 mg tablets

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

Excipient with known effect: Each tablet contains 89.60mg lactose (as lactose monohydrate)

For the full list of excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Tablet

White oval, biconvex snap tab tablet, one side scored, other side marked "E H"

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 medications.

This fixed dose combination is not suitable for initial therapy.

### 4.2 Posology and method of administration

#### Posology

The dosage of Enalapril / Hydrochlorothiazide 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 Enalapril / Hydrochlorothiazide; 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 Enalapril / Hydrochlorothiazide.

##### *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  $>30$  and  $<80$  ml/min, Enalapril / Hydrochlorothiazide should be used only after titration of the individual components.

##### *Use in the 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 has 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  $\leq 30$  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 sections 4.4 and 4.6).
- Severe hepatic impairment.
- Stenosis of the renal arteries.
- The concomitant use of Enalapril / Hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR  $< 60$  ml / min /  $1.73$  m<sup>2</sup>) (see sections 4.5 and 5.1).
- Combination with sacubitril/valsartan due to the increased risk of angioedema. Do not administer Enalapril / Hydrochlorothiazide 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 / Hydrochlorothiazide**

*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.

#### Hypotension and electrolyte fluid imbalance

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril / Hydrochlorothiazide, symptomatic hypotension is more likely to occur if the patient is volume-depleted e.g., by diuretic therapy, dietary salt restrictions, 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 disease 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 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 functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of Enalapril / Hydrochlorothiazide 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 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 contraindication 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 systematic blood pressure may occur with Enalapril / Hydrochlorothiazide. 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 / Hydrochlorothiazide may be necessary.

#### Renal functional 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.

Enalapril / Hydrochlorothiazide should not be administered to patients with renal insufficiency (creatinine clearance < 80 ml/min and >30 ml/min) until titration of enalapril dosage 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, Renal function impairment; Hydrochlorothiazide, Renal function impairment in section 4.4). If this occurs, therapy with Enalapril / Hydrochlorothiazide should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see Special warnings and precautions for use. Enalapril, 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, hyperkalemia 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, Hyperkalaemia in section 4.4).

#### Lithium

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

#### Lactose

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

#### Paediatric population

The 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 recognised 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 / 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<sup>®</sup>) 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, periodical 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 inhibitor, including enalapril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events in particular dehydration, acute cardiac decompensation, metabolic acidosis, hypoaldosteronism or those using concomitant 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 co-trimoxazole). The use of potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes, or other drugs that may lead to a significant increase in serum potassium. Hyperkalemia 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 is recommended (see Special warnings and precautions for use, Enalapril /

Hydrochlorothiazide, Hyperkalaemia; 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

**Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus).**

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

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, enalapril / hydrochlorothiazide 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 taking ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks. However, in general it appears that black patients 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 also section 4.3).

Patients receiving concomitant ACE inhibitor and neprilysin inhibitor therapy (e.g., sacubitril, racecadotril) may be at increased risk for angioedema (see section 4.5). 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 sulfate have experienced life-threatening anaphylactoid 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 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 (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**

#### 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 / Hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

#### 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 / Hydrochlorothiazide, Renal function impairment; Enalapril Maleate, Renal function impairment in section 4.4).

Enalapril / Hydrochlorothiazide should not be administered to patients with renal insufficiency (creatinine clearance  $\leq$ 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet.

#### Hepatic impairment

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 adjustments 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 have been associated with thiazide diuretic therapy; however, at the 12.5 mg dose of hydrochlorothiazide contained in Enalapril / 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.

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, an 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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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 minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

## **4.5 Interaction with other medicinal products and other forms of interaction**

### **Enalapril / 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 nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

#### Lithium

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

Use of Enalapril / Hydrochlorothiazide 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.

*Co-trimoxazole (trimethoprim/sulfamethoxazole)*

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

**Enalapril Maleate**

*Potassium-sparing diuretics, 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, potassium-containing salt substitutes, or other drugs that may increase serum potassium (e.g. heparin, trimethoprim-containing products such as co-trimoxazole) 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 effect can be reduced by discontinuation of the diuretic, 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

Patients taking concomitant mTOR inhibitors (e.g. temsirolimus, sirolimus, everolimus) therapy may be at 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). 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).

#### 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).

#### Acetylsalicylic acid, thrombolytics and beta-blockers

Enalapril can be safely administered concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics and betablockers.

#### **Hydrochlorothiazide**

#### Non-depolarising Muscle Relaxants

Thiazides may increase the responsiveness to tubocurarine.

#### Alcohol, barbiturates or opioid analgesics

Potential 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 gastrointestinal 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 hypokalemia.

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 Enalapril / Hydrochlorothiazide in breast-feeding is not recommended for preterm infants and for the first few weeks after delivery, because of hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In case of an older

infant the use of Enalapril /Hydrochlorothiazide 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 Enalapril / Hydrochlorothiazide during breast-feeding is not recommended. If Enalapril / Hydrochlorothiazide 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 side effects have been reported for Enalapril / Hydrochlorothiazide, enalapril alone or hydrochlorothiazide alone either during clinical studies or after the drug was marketed.

The evaluation of adverse reactions is based on the following information on frequencies:

Very common ( $\geq 1/10$ )

Common: ( $\geq 1/100$  to  $< 1/10$ )

Uncommon: ( $\geq 1/1,000$  to  $< 1/100$ )

Rare: ( $\geq 1/10,000$  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)**

not known: Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)

**Blood and Lymphatic System Disorders**

uncommon: anaemia (including aplastic and haemolytic)

rare: neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases

**Endocrine disorders**

not known: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

**Metabolism and Nutrition Disorders**

common: hypokalaemia, increase of cholesterol, increase of triglycerides, hyperuricemia

uncommon: hypoglycaemia (see section 4.4), hypomagnesemia, gout\*\*

rare: increase in blood glucose

very rare: hypercalcemia (see section 4.4)

**Nervous System and Psychiatric Disorders**

common: headache, depression, syncope, taste alteration

uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, decreased libido\*\*

rare: dream abnormality, sleep disorders, paresis (due to hypokalaemia)

**Eye Disorders**

very common: blurred vision

not unknown: choroidal effusion

**Ear and Labyrinth Disorders**

uncommon: tinnitus

**Cardiac and Vascular Disorders:**

very common: dizziness

common: hypotension, orthostatic hypotension, rhythm disturbances, angina pectoris, tachycardia

uncommon: flushing, palpitations, myocardial infarction or cerebrovascular accident\*, possibly secondary to excessive hypotension in high risk patients (see section 4.4)

rare: Raynaud's phenomenon

**Respiratory, Thoracic and Mediastinal Disorders**

very common: cough

common: dyspnoea

uncommon: rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma

rare: pulmonary infiltrates, respiratory distress (including pneumonitis and pulmonary oedema), rhinitis, allergic alveolitis/eosinophilic pneumonia  
Very rare: Acute respiratory distress syndrome (ARDS) (see section 4.4)

### **Gastrointestinal Disorders**

very common: nausea  
common: diarrhoea, abdominal pain  
uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer, flatulence\*\*  
rare: stomatitis/aphthous ulcerations, glossitis  
very rare: intestinal angioedema

### **Hepatobiliary Disorders**

rare: 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**

common: rash (exanthema), hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4).  
uncommon: diaphoresis, pruritus, urticaria, alopecia  
rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus  
not known: 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**

common: muscle cramps  
uncommon: arthralgia\*\*

### **Renal and Urinary Disorders**

uncommon: renal dysfunction, renal failure, proteinuria  
rare: oliguria, interstitial nephritis

### **Reproductive System and Breast Disorders**

uncommon: impotence  
rare: gynaecomastia

### **General Disorders and Administration Site Conditions**

very common: asthenia  
common: chest pain, fatigue  
uncommon: malaise, fever

### **Investigations**

common: hyperkalaemia, increases in serum creatinine

uncommon: increases in blood urea, hyponatremia  
rare: elevations of liver enzymes, elevations of serum bilirubin

\*Incidence rates were comparable to those in the placebo and active control groups in the clinical trial.

\*\*Only seen with doses of hydrochlorothiazide 12.5 mg and 25 mg.

#### **Description of Selected Adverse Reactions**

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide 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 at [www.mhra.gov.uk/yellowcard](http://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 Enalapril /Hydrochlorothiazide. Treatment is symptomatic and supportive. Therapy with Enalapril / Hydrochlorothiazide 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 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.

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**

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: ACE inhibitors, 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 of 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 / 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 hydrochlorothiazide 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 hydrochlorothiazide use ( $\geq 50,000$  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 hydrochlorothiazide: 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 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%. 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 is not influenced by the presence of food in the gastrointestinal 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 5 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 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 hours 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 1 mother and 10mg in 2 mothers; enalapril levels were not determined.

### **5.3 Preclinical safety data**

No relevant information.

## **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 Al/PA/Al/PVC blisters which are inserted into a carton.

Pack sizes: 10, 14, 20, 28, 30, 49, 50, 50x1, 60, 98, 100 tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements for disposal.

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

**7      MARKETING AUTHORISATION HOLDER**

Pharmapoint UK Ltd  
30 Hatfeild Mead  
Morden, Surrey  
SM4 5PE  
United Kingdom

**8      MARKETING AUTHORISATION NUMBER(S)**

PL 45816/0001

**9      DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

21/03/2025

**10     DATE OF REVISION OF THE TEXT**

21/03/2025