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LAY SUMMARY

The MHRA granted Roger Oakes Limited a Marketing Authorisation (licence) for the medicinal product Enalapril/Hydrochlorothiazide 20mg/12.5mg Tablets on 15 November 2010. This product is available as a prescription-only medicine (POM) for the treatment of high blood pressure (hypertension). It is intended to replace the combination of 20mg enalapril maleate and 12.5mg hydrochlorothiazide in patients who have been stabilised on the separate medications given in the same proportions. It can also be used in situations where treatment with enalapril alone has not provided sufficient reduction in blood pressure.

This medicine contains enalapril maleate and hydrochlorothiazide. Enalapril maleate is one of a group of medicines known as Angiotensin-Converting Enzyme (ACE) Inhibitors. These work by expanding your blood vessels making it easier for your heart to pump blood to your body. Hydrochlorothiazide (HCT) is one of a group of medicines known as diuretics. These work by increasing the volume of urine you produce, therefore reducing the water content of your blood and in turn the volume of blood circulating in your body.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Enalapril/Hydrochlorothiazide 20/12.5mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.
ENALAPRIL/HYDROCHLOROTHIAZIDE 20MG/12.5MG TABLETS
PL 32019/0005

SCIENTIFIC DISCUSSION

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Pharmaceutical assessment Page 5
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Overall conclusions and risk benefit assessment Page 10
INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Enalapril/Hydrochlorothiazide 20mg/12.5mg Tablets (PL 32019/0005) to Roger Oakes Limited on 15 November 2010. This product is available as a prescription-only medicine (POM) for the treatment of essential hypertension. This fixed-dose combination:

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

This product contains the active ingredients enalapril maleate and hydrochlorothiazide. Enalapril maleate is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase, which catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma rennin activity (due to removal of negative feedback of rennin release), and decreased aldosterone secretion. ACE is identical to kininase II. Thus, enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.

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

The application was submitted as simple abridged application according to Article 10c (formerly Article 10.1(a)(ii)) of Directive 2001/83/EC, cross-refering to Enalapril/Hydrochlorothiazide 20/12.5mg Tablets (PL 11311/0265), which was approved on 03 June 2004 to the marketing authorisation holder Tillomed Laboratories Limited.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.
1. INTRODUCTION
This is a simple, piggyback application for Enalapril/Hydrochlorothiazide 20mg/12.5mg Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Rutland, LE15 7NF.

The application cross-refers to Enalapril/Hydrochlorothiazide 20/12.5mg tablets (PL 11311/0265), approved on 03 June 2004 to the marketing authorisation holder Tillomed Laboratories Limited.

The current application is considered valid.

2. MARKETING AUTHORIZATION APPLICATION FORM

2.1 Name(s)
The proposed name of the product is Enalapril/Hydrochlorothiazide 20mg/12.5mg Tablets. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each tablet contains enalapril maleate 20mg and hydrochlorothiazide 12.5mg. The product is stored in aluminium/polyamide/polyvinylchloride blister strips, which are inserted into a carton folder in pack sizes of 10, 14, 20, 28, 30, 49, 50, 50x1, 60, 98 and 100 tablets.

Not all pack sizes may be marketed. However, the marketing authorisation holder has committed to submitting mock-ups of the packaging for any pack size to the relevant regulatory authorities for approval before marketing.

The proposed shelf-life (3 years) with the special storage conditions ‘Do not store above 30°C. Store in the original package in order to protect from moisture.’ are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the product will be available as a prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Rutland, LE15 7NF.

The QP responsible for pharmacovigilance is stated.
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. Confirmation has been provided from the supplier of lactose monohydrate that the lactose is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms are used in the manufacture of the finished product. This is consistent with the cross-reference product.

3. EXPERT REPORTS
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the products is identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL)/CARTON
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured.
and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.
PRECLINICAL ASSESSMENT

As this application is identical to the reference product Enalapril/Hydrochlorothiazide 20mg/12.5 mg Tablets (PL 11311/0265), no new preclinical data have been supplied with this application and none are required.

A preclinical expert report has been written by a suitably qualified person and is satisfactory.

The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

As this application is identical to the reference product Enalapril/Hydrochlorothiazide 20mg/12.5 mg Tablets (PL 11311/0265), no new clinical data have been supplied with this application and none are required.

The MAH has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for this application are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data are submitted and none are required for an application of this type.

EFFICACY
This application is identical to the previously granted application for Enalapril/Hydrochlorothiazide 20mg/12.5 mg Tablets (PL 11311/0265).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Colour mock-ups of the labelling have been provided and are satisfactory. The approved labelling artwork complies with statutory requirements. The name of the product in Braille appears on the outer packaging.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with enalapril maleate and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk is, therefore, considered to be positive.
**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 19/02/2009.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 10/03/2009.</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information on 20/05/2009, 02/02/2010 and 23/06/2010 and 01/11/2010.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 21/12/2009, 21/05/2010, 20/10/2010 and 01/11/2010.</td>
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<td>5</td>
<td>The application was determined on 01/11/2010.</td>
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ENALAPRIL/HYDROCHLOROTHIAZIDE 20MG/12.5MG TABLETS
PL 32019/0005

STEPS TAKEN AFTER ASSESSMENT

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<th>Date submitted</th>
<th>Application type</th>
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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 enalapril maleate 20 mg and hydrochlorothiazide 12.5 mg.
Excipient: Each tablet contains lactose monohydrate
For a 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
Enalapril maleate/Hydrochlorothiazide 20 mg/12.5 mg can be administered in a single dose/day with or without food.
Individual dose titration with both active substances can be recommended.
When clinically appropriate, direct change from ACE inhibitor monotherapy to the fixed combination may be considered.

Dosage in patients with normal renal function
The usual dosage is one tablet, taken once daily.

Dosage in renal insufficiency
- Creatinine clearance ≥ 30 ml/min: The dose of enalapril should be titrated in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min before switching to the fixed combination. Loop diuretics are preferred to thiazides in this population. The dose of enalapril maleate and hydrochlorothiazide should be kept as low as possible (see section 4.4).

Potassium and creatinine should be monitored periodically in these patients, e.g. every 2 months when the treatment has been stabilised (see section 4.4).

- Creatinine clearance < 30 ml/min: see section 4.3.

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

Use in the elderly
The use in the elderly has been shown to be as good as in younger hypertensive patients. In case of physiological renal impairment, titration with the monocomponent enalapril is recommended prior to using the fixed combination.
Use in children and adolescents (< 18 years)
Safety and effectiveness of Enalapril maleate/Hydrochlorothiazide 20 mg/12.5 mg in children has not been established.

4.3 Contraindications
Associated with enalapril:
This medicinal product must not be used in patients with:
● hypersensitivity to enalapril, other ACE-inhibitors or to any of the excipients
● a history of angioedema (Quincke’s oedema) linked to previous treatment with an ACE inhibitor and/or in patients with inherited or idiopathic angioedema
● 2nd and 3rd trimesters of pregnancy (see section 4.4 and 4.6)

Associated with hydrochlorothiazide:
This medicinal product must not be used in patients with:
● hypersensitivity to hydrochlorothiazide or other sulphonamides
● severe renal impairment (creatinine clearance <30 ml/min)
● severe hepatic impairment/hepatic encephalopathy
● 2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
● lactation

4.4 Special warnings and precautions for use
ASSOCIATED WITH THE EXCIPIENTS
This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

ASSOCIATED WITH ENALAPRIL
Symptomatic hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving enalapril, symptomatic hypotension is more likely to occur if the patient is volume-depleted or has electrolyte imbalance which may occur due to diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting (see section 4.5).

In 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, hyponatraemia or renal dysfunction. In these patients, therapy must be started under medical supervision preferably in a hospital and the patients must be followed closely whenever the dose of enalapril and/or diuretic is adjusted.

Similar considerations may apply 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.

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 at reduced doses or either of the active substances may be used appropriately alone 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. This effect is anticipated and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or enalapril may be necessary.

Aortic stenosis/hypertrophic cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular or aortic outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.
Renal function impairment
In cases of renal impairment (creatinine clearance < 80 ml/min), the initial enalapril dosage should be adjusted according to the patient’s creatinine clearance (see section 4.2) and then as a function of the patient’s response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

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.

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. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see section 4.4. – renovascular hypertension).

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

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

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

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia rarely occurs. 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.

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. This may occur at any time during treatment. In such cases, enalapril should be discontinued promptly, and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips, the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

Angioneurotic oedema associated with laryngeal edema may be fatal. 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.

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)

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

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

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

*Diabetic patients*
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should closely be monitored during the first month of treatment with an ACE inhibitor. (see section 4.5)

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

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

*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.

*Interactions*
This medicinal product IS GENERALLY NOT RECOMMENDED in combination with potassium-sparing diuretics, potassium salts and estramustine (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).

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

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 balances may precipitate hepatic encephalopathy in patients with hepatic disease. In this case, treatment with the diuretic must be stopped immediately.

Enalapril maleate/Hydrochlorothiazide 20 mg/12.5 mg is generally not recommended in combination with sulthiame (see section 4.5).

ASSOCIATED WITH ENALAPRIL AND HYDROCHLOROTHIAZIDE

Interaction

This medicinal product is generally not recommended in combination with lithium due to the potential of lithium toxicity (see section 4.5).

Precautions for use

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Fluid/electrolyte balance

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

Thiazides (including hydrochlorothiazide) can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with enalapril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

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

Natraemia

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

Kalaemia

Potassium depletion and hypokalaemia are the major risks associated with thiazide and related diuretics. Hypokalaemia (< 3.5 mmol/l) must be prevented in certain at-risk populations, such as elderly and/or malnourished patients, especially when receiving combination therapy, cirrhotic patients with oedema and ascites, coronary patients, patients with heart failure. In these cases, hypokalaemia increases the cardiotoxicity of digitalis glycosides and the risk of arrhythmia.

In patients with a long QT interval, whether congenital or substance-induced, hypokalaemia increases the risk of severe arrhythmia, in particular potentially fatal torsade de pointes, especially in patients with bradycardia.
Potassium levels must be regularly monitored, starting in the first week of treatment.

**Calcemia**
Thiazide may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium.

Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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

**Metabolic and endocrine effects**
Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. The salt and volume depletion caused by thiazides reduces the urinary elimination of uric acid. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

**Renal impairment**
Thiazide diuretics are fully efficacious only in patients with normal renal function or mild renal impairment (evaluated, for example, according to creatinine clearance). In the elderly, the value for creatinine clearance must be adjusted for age, weight and sex.

Hypovolaemia, secondary to diuretic-induced fluid and sodium loss at the beginning of treatment, leads to reduced glomerular filtration. This can cause an increase in blood urea and creatinine. This transient functional renal impairment is without consequence in patients with normal renal function, but can aggravate pre-existing renal impairment.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotaemia. Cumulative effects of the drug may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

**Athletes/anti-doping test**
The attention of athletes is drawn to the fact that this medicinal product contains an active substance which may induce a positive reaction in anti-doping tests.

**Other**
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

**ASSOCIATED WITH ENALAPRIL AND HYDROCHLOROTHIAZIDE**

**Functional renal impairment**
Some hypertensive patients with no apparent pre-existing renal disease have developed signs of functional renal impairment. If this occurs, treatment must be discontinued. Reinstitution of therapy at reduced dosage may be possible, or either of the components may be used appropriately alone.

**Hypotension and fluid/electrolyte imbalance**
Patients must be systematically monitored for clinical signs of fluid/electrolyte imbalance, which may occur during intercurrent diarrhoea or vomiting. Regular monitoring of plasma electrolytes must be undertaken in such patients.

Significant hypotension may require the initiation of intravenous isotonic saline.
Transient hypotension is not a contra-indication to continued treatment. After volume repletion and establishment of satisfactory blood pressure, treatment can be reinstituted, either at a lower dosage or either of the components may be used appropriately alone.

Risk of hypokalaemia
The combination of an ACE inhibitor and non-potassium-sparing diuretic does not preclude the development of hypokalaemia, in particular in diabetic or renally impaired patients. Plasma potassium must be regularly monitored.

Paediatric use
The safety and efficacy of this product have not been demonstrated in controlled studies in children.

4.5 Interaction with other medicinal products and other forms of interaction
RELATED TO ENALAPRIL

Potassium-sparing diuretics and potassium supplements
ACE inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring serum potassium (see section 4.4).

Diuretics (thiazides or loop diuretics)
Prior treatment with high-dosed diuretics may result in volume depletion and thus in a risk of hypotension when initiating therapy with enalapril (see section 4.4). The hypotensive effect can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

Other antihypertensive agents
Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with glyceryl trinitrate 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 increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

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

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid = 3g/day
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

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

Gold
Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness and hypotension, which can be very severe) following injectable gold (for example, sodium aurothiomaalate) have been reported more frequently in patients receiving ACE inhibitor therapy.

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

Alcohol
Alcohol enhanced the hypotensive effect of ACE inhibitors

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates
Enalapril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, betablockers and/or nitrates.

RELATED TO HYDROCHLOROTHIAZIDE
Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin):
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive drugs
Additive effect.

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.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.

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

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

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

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

Cytotoxic agents (eg cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates
In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.
Methyldopa
There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

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

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Enalapril/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulthiopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphenamid, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

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

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

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

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

Amphotericin B (parenteral), corticosteroids, ACTH or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Pregnancy and lactation

Pregnancy
Enalapril

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative 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.
ACE inhibitor therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also 5.3 “Preclinical safety data”). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see also section 4.3 and 4.4).

**Hydrochlorothiazide**
This fixed combination is not recommended in the first trimester of pregnancy and contra-indicated in the second and third trimesters (see section 4.3).

Diuretics may give rise to fetoplacental ischemia with the attendant risk of fetal hypotrophy. Rare cases of severe neonatal thrombocytopenia have been reported.

Hydrochlorothiazide should not be used for pregnancy oedema of (pre)eclampsia, due to risk of decreased plasma volume and placental hypoperfusion, without a positive effect on the disease.

**Lactation**
The administration of this drug is contraindicated during lactation.

**Enalapril**
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant the use of enalapril in breastfeeding 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 in 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 breast milk

Thiazides during breast feeding have been associated with decrease or even suppression of milk lactation. Hypersensitivity to sulphonamide-derived drugs, hypokalaemia and nuclear icterus might occur

Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of this therapy for the mother.

### 4.7 Effects on ability to drive and use machines
When driving vehicles or operating machines it should be taken into account that occasionally vertigo or fatigue may occur (see section 4.8).

### 4.8 Undesirable effects
The evaluation of adverse reactions is based on the following information on frequencies:

- **Very common** (≥ 1/10)
- **Common:** (≥ 1/100 up to < 1/10)
- **Uncommon:** (≥ 1/1.000 up to < 1/100)
- **Rare:** (≥ 1/10.000 up to < 1/1.000)
- **Very rare:** (< 1/10.000)
- **Not known** (Frequency on the basis of available data not assessable)

**RELATED TO ENALAPRIL**

**Blood and lymphatic system disorders:**
- uncommon: anaemia (including aplastic and haemolytic)
- rare: neutropenia, decreases in haemoglobin, decreases in haematocrit, thrombocytopenia, agranulocytosis, myelosuppression, pancytopenia, lymphadenopathy, autoimmune diseases.
Metabolic and nutrition disorders:
uncommon: hypoglycemia (see section 4.4 ‘diabetic patients’).

Nervous system disorders:
common: headache, depression
uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo
rare: dream abnormality, sleep disorders

Eye disorders:
very common: blurred vision.

Cardiac and vascular disorders:
very common: dizziness
common: hypotension (including orthostatic hypotension), syncope, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in risk patients (see section 4.4), chest pain, rhythm disorders, angina pectoris, tachycardia
uncommon: orthostatic hypotension, palpitations
rare: Raynaud's syndrome.

Respiratory, thoracic and mediastinal disorders:
very common: cough
common: dyspnoea
uncommon: rhinorrhoea, sore throat and hoarseness, bronchospasm/asthma
rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:
very common: nausea
common: diarrhoea, abdominal pain, taste alteration
uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer
rare: stomatitis/aphthous ulcerations, glossitis.
very rare: intestinal angioedema

Hepatobiliary disorders:
rare: hepatic failure, hepatitis - either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice).

Skin and subcutaneous tissue disorders:
common: rash, hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see section 4.4).
uncommon: diaphoresis, pruritus, urticaria, alopecia
rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma

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

Renal and urinary disorders:
uncommon: renal dysfunction, renal failure, proteinuria
rare: oliguria.

Reproductive system and breast disorders:
uncommon: impotence
rare: gynaecomastia.

General disorders and administration site conditions:
very common: asthenia
common: fatigue
uncommon: muscle cramps, flushing, tinnitus, malaise, fever.

Investigations:
common: hyperkalaemia, increases in serum creatinine
uncommon: increases in blood urea content, hyponatraemia
rare: elevations of liver enzymes, elevations of serum bilirubin.

RELATED TO HYDROCHLOROTHIAZIDE
Infections and infestations:
sialadenitis

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

Metabolism and nutrition disorders:
anorexia, hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including
hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides

Psychiatric disorders:
restlessness, depression, sleep disturbances

Nervous system disorders:
loss of appetite, paraesthesia, light-headedness

Eye disorders:
xanthopsia, transient blurred vision

Ear and labyrinth disorders:
vertigo

Cardiac disorders:
potural hypotension, cardiac arrhythmias

Vascular disorders:
necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders:
respiratory distress (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders:
gastric irritation, diarrhoea, constipation, pancreatitis

Hepato-biliary disorders:
jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders:
photosensitivity reactions, rash, cutaneous lupus erythematosus-like reactions, reactivation of
cutaneous lupus erythematous, urticaria, anaphylactic reactions, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:
muscle spasm

Renal and urinary disorders:
renal dysfunction, interstitial nephritis

General disorders and administration site conditions:
fever, weakness
4.9 Overdose

No specific information is available with respect to the treatment of an overdose of Enalapril maleate/Hydrochlorothiazide 20 mg/12.5 mg. Symptoms of overdose are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

ASSOCIATED WITH ENALAPRIL

Limited data are available on overdose in humans.

**Symptoms**

The most prominent features of overdose reported to date are marked hypotension beginning some six hours after ingestion of the tablets, concomitant with blockade of the renin-angiotensin system, and stupor.

Symptoms associated with overdose of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril respectively.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

The signs of acute intoxication are primarily related to fluid/electrolyte imbalance (hyponatramia, hypokalaemia).

In addition to the expected diuresis, overdose of thiazides may produce varying degrees of lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function, and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown.

Gastrointestinal irritation as well as an increase of blood urea nitrogen (BUN) were reported, and especially in patients with impaired renal function it can come changes of the serum electrolytes. Clinically, nausea, vomiting, hypotension, cramps, dizziness, somnolence, confusional states, polyuria or oliguria to the point of anuria (through hypovolaemia) may occur.

**COMBINATION**

Treatment is symptomatic and supportive. Treatment with Enalapril maleate/Hydrochlorothiazide 20 mg/12.5 mg should be discontinued and the patient should be carefully monitored. Recommended measures include induction of vomiting, administration of activated charcoal and administration of a laxative and/or gastric lavage if the tablets were taken recently. Any dehydration, disturbances in the electrolyte balance and hypotension should be treated in an appropriate manner. Enalaprilat can be eliminated from blood circulation via haemodialysis (see section 4.4). The extent to which hydrochlorothiazide is removed is not established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, combinations

ATC-Code: C09B A02

**Pharmacological mechanism of action**

ASSOCIATED WITH ENALAPRIL

Enalapril maleate is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyses the conversion of angiotensin I to the pressor substance angiotensin II.

After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma rennin activity (due to removal of negative feedback of rennin release), and decreased aldosterone secretion.

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

Hydrochlorothiazide is a thiazide diuretic which acts as by inhibiting fluid-expelling and blood pressure-lowering agent which increase the tubular re-absorption of sodium in the cortical diluting segment.

It increases the urinary excretion of sodium and chloride and, to a lesser degree, the excretion of potassium and magnesium, thus increasing diuresis and exerting an anti-hypertensive effect.

Characteristics of the antihypertensive therapy

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

Administration of enalapril to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of enalapril has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and haemodynamic effects have been shown to be maintained for at least 24 hours.

In haemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of enalapril there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pre-treatment glomerular filtration rates, the rates were usually increased.

In short-term clinical studies in diabetic and non-diabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

When given together with thiazide-type diuretics, the blood pressure-lowering effects of enalapril are at least additive. Enalapril may reduce or prevent the development of thiazide-induced hypokalaemia.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

The time to onset of diuretic activity is approximately 2 hours. Diuretic activity reaches a peak after 4 hours and is maintained for 6 to 12 hours.

Above a certain dose, thiazide diuretics reach a plateau in terms of therapeutic effect whereas adverse reactions continue to multiply. When treatment is ineffective, increasing the dose beyond recommended doses serves no useful purpose and often gives rise to adverse reactions.

ASSOCIATED WITH THE COMBINATION

In clinical studies, the concomitant administration of enalapril and hydrochlorothiazide reduced blood pressure more significantly than either substance alone.

The administration of enalapril inhibits the renin-angiotensin-aldosterone system and tends to reduce the hydrochlorothiazide-induced potassium.

Combination of an ACE inhibitor with a thiazide diuretic produces a synergistic effect and also lessens the risk of hypokalaemia provoked by the diuretic alone.
5.2 Pharmacokinetic properties
Co-administration of enalapril and hydrochlorothiazide in various doses has little or no effect on the bioavailability of these two substances.

ASSOCIATED WITH ENALAPRIL

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

Distribution
Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of enalapril maleate. The effective half-life for accumulation of enalapril following concentrations of enalaprilat were reached after four days of treatment.

Over the range of concentrations which are therapeutically relevant, enalapril binding to human plasma proteins does not exceed 60%.

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 breastfed infant would be about 0.16% of the maternal weight-adjusted dosage.

A woman who had been taking oral enalapril 10 mg daily for 11 months had peak enalapril milk levels of 2 µg/L 4 hours after a dose and peak enalaprilat levels of 0.75 µg/L about 9 hours after the dose. The total amount of enalapril and enalaprilat measured in milk during the 24 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.

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

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

Renal impairment
The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 ml/min) steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 ml/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed. (See section 4.2, Dosage in renal Insufficiency).

Enalaprilat may be removed from the general circulation by hemodialysis. The dialysis clearance is 62 ml/min.

ASSOCIATED WITH HYDROCHLOROTHIAZIDE

Absorption
Oral absorption of hydrochlorothiazide is relatively rapid. The bioavailability of hydrochlorothiazide varies between 60 and 80%. The time to peak plasma concentration (Tmax) varies between 1.5 and 5 hours, with a mean of about 4 hours.
Distribution
Protein binding is approximately 40%.
The mean plasma half-life in fasted individuals has been reported to be 5 to 15 hours.

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

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

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation.

The compound has been shown to cross the placenta and is secreted in milk.

Angiotensin converting enzyme inhibitors, as a class, have been shown to be fetotoxic (causing injury and/or death to the fetus) when given in the second or third trimester.

Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
calcium hydrogen phosphate, dihydrate
lactose monohydrate
magnesium stearate
maize starch
sodium hydrogen carbonate
talc

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container
The tablets are packed in Al/PA/Al/PVC blisters which are inserted into a carton folder.
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
Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Roger Oakes Ltd
Allstoe House
Church Lane
Greetham
Rutland LE15 7NF
8 MARKETING AUTHORISATION NUMBER(S)
PL 32019/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/11/2010

10 DATE OF REVISION OF THE TEXT
15/11/2010
Enalapril/Hydrochlorothiazide 20/12.5mg Tablets

**Please read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and should not be passed on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. **What this medicine is and what it is for**

Enalapril + HCT Tablets contain Enalapril Maleate and Hydrochlorothiazide. Enalapril Maleate is one of a group of medicines known as ACE (Angiotensin Converting Enzyme) inhibitors. These work by expanding your blood vessels making it easier for your heart to pump blood to your body. Hydrochlorothiazide (HCT) is one of a group of medicines known as Diuretics. These work by increasing the volume of urine you produce, therefore reducing the water content of your blood and in turn the volume of blood circulating through your body.

Enalapril + HCT Tablets are used in the treatment or prevention of high blood pressure (hypertension). It is intended for the combination treatment of 20mg Enalapril Maleate and 12.5mg Hydrochlorothiazide in patients who have been stabilized on the separate medications given in the same proportions. It is not suitable for initial therapy.

2. **Before you take**

Do not take Enalapril + HCT Tablets:

- If you are allergic (hypersensitive) to Enalapril Maleate, Hydrochlorothiazide, other Sulphonamides, other ACE Inhibitors or any of the other ingredients in the tablets (these are listed in Section 6. Further information).
- If you have been told by your doctor that you have a kidney problem.
- If you suffer from severe kidney problems.
- If you are taking diuretics for gout.
- If you already have a kidney transplant.
- If you are less than 18 months pregnant (It is not recommended to use early pregnancy - see pregnancy section).
- If you are breastfeeding (See pregnancy and breast-feeding section).

Take special care with Enalapril + HCT - Tell your doctor if any of the following apply to you:

- If you are due to have a surgical operation. You may need to stop taking your medicine.
- If you have diabetes.
- If you suffer from hereditary or severe kidney problem.
- If you suffer from kidney problems.
- If you suffer from liver problems.
- If you suffer from anaemia, fever, joint pain or weakness (Collagen vascular disease).
- If you have an allergy to aspirin or other similar allergy reactions which cause swelling of the face or throat (Angioedema).
- If you are receiving treatment to reduce the effect of an allergy to a wra or wra sting.
- If you are about to have a treatment to remove cholesterol from your blood (LDL Apheresis).
- If you are on dialysis.
- If you are diabetic.
- If you suffer from Lupus.
- You must tell your doctor if you think you are (or might become) pregnant. Enalapril + HCT is not recommended in early pregnancy and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

**Please note**

- If you are a patient, the hydrochlorothiazide contained in this medicine may produce a selective anti-doping effect.
- Enalapril + HCT is less effective in black population at lowering blood pressure.

Taking other medicines

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.

**Medicines which may interact**

- Certain analgesics. If you are due to have a surgical procedure, you may need to stop taking the analgesic.
- Enalapril + HCT is less effective in black population at lowering blood pressure.

Other medicines used to treat high blood pressure, e.g. Glyceryl trinitrate, hydralazine mononitrate (Nitrites), Dihydroxy (Vasoilone) and Methyldopa.

**Possible side effects**

- Medicine used to increase frequency of urination (Diuretics) e.g. Spironolactone, Eplerenone, Thiazides and Amiloride (Potassium-sparing diuretics), Berenstienmuthizide (Thiazides) and Furosemide (Lasix) in patients with hyperkalaemia.
- Medicine used for treatment of depression e.g. Amirtiapine (Tricyclics) or Venlafaxine (SNRI).
- Medicine used to treat mood disorders e.g. Lithium (Antimanic).
- Medicine used to treat diabetes e.g. insulin and sulfonylurea tablets.
- Medicine used to reduce the body’s immunity when receiving organ transplant e.g. Ciclosporin (immunosuppressants).
- Selective antibodies e.g. Aymal, Aymal Sodium, Soneryl, Prominal, Nembutal, Luminial, Turinal, Barbital (Barbiturates).
- Medicine used to treat severe pain e.g. codeine, Codeina, Morphin, Suprin, Paregoric, Pethidine (Narcotics).
- Calcium supplement e.g. Dicalaid, Calciwhey and Vitamin D.
- Medicine used to treat irritable bowel syndrome e.g. Proxamin (Cardiac Glycosides).
- Medicine used to control cholesterol levels e.g. Cholestyramine, Colestipol.
- Medicine used to treat blood hypothyroidism (LH-Thyroxin).
- Medicine used to reduce inflammation e.g. Prednisolone (Corticosteroids).
- Medicine used to treat gout e.g. Allopurinol, Probenecid and Sulfinpyrazone.
- Medicine used for the treatment of cancer & tumours e.g. Cyclophosphamide, Fluorouracil, Methotrexate (Cytostatic Agents).
- Muscle relaxants e.g. Tubocurarine.
- Non-steroidal Anti-Inflammatory Drugs (NSAIDs) e.g. Diclofenac and Aspirin (if you take more than 8 tablets a day).
- Potassium-containing supplements or salt substitutes.
- Medicine used to treat constipation e.g. Bisacodyl, Senova (Stimulant Laxatives).
- Gold therapy by injection, used for stiffness and inflammation (such as muscles, bones and joints) or rheumatoid arthritis.
- Medicine used to prevent muscle spasm e.g. Atropine Dipidide.
- Medicine used to treat mouth ulcers and sore throats e.g. Sulfadiazine.
- Carcinomazone, used to treat epilepsy.
- Amoxicillin (beta-lactamine), used to treat tooth, throat and fungal infections.
- ACTH, used to help whether your adrenal glands are working properly.
- Enalapril + HCT may interfere with certain laboratory tests e.g. Parathyroid tests.
- Tests which use high dose of iodine.

**Taking Enalapril + HCT with food and drink**

During treatment with Enalapril + HCT, it is advisable not to drink alcohol.

These tablets may be taken before, during or after meals.

**Pregnancy and breastfeeding**

You must tell your doctor if you are (or might become) pregnant. Your doctor will normally advise you to stop taking Enalapril + HCT before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Enalapril + HCT. Enalapril + HCT is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

**Breastfeeding**

Tell your doctor if you are breastfeeding or about to start breastfeeding. Breast-feeding newborn babies (first few weeks after birth) and especially premature babies, is not recommended whilst taking Enalapril + HCT. In the case of an older baby your doctor should advise you on the benefits and risks of taking Enalapril + HCT whilst breast-feeding, compared with other treatments.

**Driving and using machinery**

Enalapril + HCT Tablets can cause dizziness and tiredness. If this is experienced it is necessary to avoid driving or operating machinery or pursuing any activity which requires full attention.

**Important information about some of the ingredients of Enalapril + HCT**

Enalapril + HCT contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.
How to take

Always take Enalapril + HCT Tablets as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- Enalapril + HCT Tablets should be swallowed whole and with sufficient fluid (e.g. water). These tablets may be taken before, during or after meals.
- The tablets can be divided into equal halves.

Adults & Elderly

The recommended dose is one tablet daily.

Elderly patients with kidney problems
Your doctor will decide if you should take Enalapril + HCT or if the dose requires adjustment if you suffer from minor kidney problems. You may need to have your kidney function tested to be taken daily. Monitoring of kidney function is required.

Diuretic-treated patients
The diuretics should be discontinued 2 to 3 days before you start taking Enalapril + HCT.

Children

Enalapril + HCT Tablets are not recommended for children.

Do not change your dose unless your doctor tells you to do so.

If you take more Enalapril + HCT Tablets than you should

- If you take too many tablets, contact your doctor or nearest hospital emergency department immediately for advice. Remember to take this leaflet or any remaining tablets with you. The symptoms of overdose include kidney failure, shortness of breath or swelling of the legs.
- If you experience palpitations, increased heart rate (bradycardia/Tachycardia), dizziness (Vertigo), anxiety, cough

If you forget to take Enalapril + HCT Tablets

- Take as soon as you remember unless it is nearly time for your next dose. If you miss a dose do not take a double dose to make up for the forgotten tablet.

If you stop taking/leaving Enalapril + HCT Tablets

- It is important that you keep on taking Enalapril + HCT Tablets until the prescribed dose has finished.
- Do not stop taking the tablets even though you may feel better.
- Do not stop or change your treatment before talking to your doctor.
- If you have any further questions on the use of this product, ask your doctor or pharmacist.

Possible side effects

Like all medicines, Enalapril + HCT Tablets can cause side effects, although not everybody gets them

Some people will take many tablets, contact your doctor or nearest hospital emergency department immediately for advice. Remember to take this leaflet or any remaining tablets with you. The symptoms of overdose include kidney failure, shortness of breath or swelling of the legs.

Common side effects (affects 1-10 users in 100)
- Dizziness
- Blurred/distorted vision
- Feeling sick (Nausea)
- Coughing (will generally go after stopping treatment)

Common side effects (affects 1-10 users in 100)
- Low blood pressure (Hypotension)
- Disrupted heart rhythm (Arrhythmia)
- Heart attack (Acute Myocardial Infarction)
- Chest pain
- Stomach pain
- Loss of weight
- Eye disturbance (blindness or light-headedness)
- Dizziness
- Abdominal pain
- Abnormal sense of taste
- Headache
- Depression
- Shortness of breath or difficulty in breathing
- Increased blood potassium level and increases in other body fluids are usually detected by a blood test.
- Faster heart beat

Common side effects (affects 1-100 users in 100)
- Skin rash
- Sunburn (which may feel dry when you stop taking)
- Feeling of dizziness or 'spinning'

Other side effects (affects less than 1 user in 10,000)
- Fainting, swelling of the salivary gland, due to a bacterial infection
- High blood sugar levels (Hyperglycaemia)
- Oozing
- Other causes of local swelling or oedema
- Abnormal sensitivity to sunlight and other effects on the skin

Other side effects related to Hydrochlorothiazide include:
- Painful swelling of the ankles
- Weakness
- Eye condition that causes objects to appear yellow
- Muscle weakness
- Muscle spasm
- Inflammation of the kidneys which can cause swelling
- Reduced blood pressure

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

How to use

Keep out of the reach and sight of children.

It is important that you keep on taking Enalapril + HCT Tablets until the prescribed dose has finished.

If you stop taking the tablets even though you may feel better.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

Other active substances in Enalapril + HCT Tablets

Enalapril and Hydrochlorothiazide. Each tablet contains Enalapril maleate 20mg and hydrochlorothiazide 12.5mg.

What Enalapril + HCT looks like and contents of the pack

Enalapril + HCT Tablets are white, oval, uncoated, oblong tablets, with one side scored and the other side marked with "5/5".

Enalapril + HCT are available in:

- In 10, 14, 20, 28, 30, 49, 50, 50x1, 60, 90, 100

Product License Number: PL-2019/0005

The leaflet was last revised in December 2009.
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