ENALAPRIL MALEATE 5MG TABLETS
ENALAPRIL MALEATE 10MG TABLETS
ENALAPRIL MALEATE 20MG TABLETS

UKPAR

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The MHRA granted Medreich plc Marketing Authorisations (licences) for the medicinal products Enalapril Maleate 5, 10 and 20mg Tablets (PL 21880/0003-5) on 5th June 2009. These prescription-only medicines (POM) are prescribed to patients for one of the following reasons:

- Their blood pressure is too high
- They have a heart condition sometimes referred to as “heart failure”. This means that their heart is not working as well as it used to, in order to pump blood around their body, leading to tiredness after light exercise, breathlessness and swelling of the ankles and legs.
- They have damaged heart muscle, but have no symptoms.

The active ingredient enalapril maleate belongs to a group of medicines known as ACE inhibitors (drugs that lower blood pressure). These medicines work by widening the blood vessels to make it easier for the heart to pump blood through them to all parts of the body.

These applications are identical to a previously granted licence applications for Enalapril Maleate 5, 10 and 20mg Tablets (PL 18224/0024-26), which were granted to Karib Kemi Pharma Limited on 23rd December 2004.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Enalapril Maleate 5, 10 and 20mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Medreich plc Marketing Authorisations (licences) for the medicinal product Enalapril Maleate 5, 10 and 20mg Tablets (PL 21880/0003-5) on 5th June 2009. These prescription-only medicines (POM) are indicated for the following:

• Treatment of Hypertension
• Treatment of Symptomatic Heart Failure
• Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤ 35%).

These applications were submitted as simple abridged applications according to Article 10.1(c) of Directive 2001/83/EC, cross-referring to Enalapril Maleate 5, 10 and 20mg Tablets (PL 18224/0024-26), which were granted to Karib Kemi Pharma Limited on 23rd December 2004.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PAR was generated.

The products contain the active substance enalapril maleate. 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 that catalyses the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolysed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 21880/0003-5
PROPRIETARY NAME: Enalapril Maleate 5, 10 and 20mg Tablets
ACTIVE(S): Enalapril maleate
COMPANY NAME: Medreich plc
E.C. ARTICLE: Article 10 (c) of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION
These are simple abridged applications for Enalapril Maleate 5, 10 and 20mg Tablets submitted under Article 10 (c) of Directive 2001/83/EC. The proposed MA holder is Medreich plc, 9 Royal Parade, Kew Gardens, Surrey TW9 3QD, United Kingdom.

These applications refer to Marketing Authorisations for Enalapril Maleate 5, 10 and 20mg Tablets (PL 18224/0024-26), which were granted to Karib Kemi Pharma Limited on 23rd December 2004.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the products are Enalapril Maleate 5, 10 and 20mg Tablets. The products have been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products contain enalapril maleate, equivalent to 5, 10 or 20mg. The product will be packaged into PVC/aluminium foil blisters containing 28 tablets.

2.3 Legal status
The products are available as a prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation holder is Medreich plc, 9 Royal Parade, Kew Gardens, Surrey TW9 3QD, United Kingdom.

The QP responsible for pharmacovigilance is stated and a CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

A flow diagram showing the sequence and activities of the different sites involved in the manufacturing process has been provided.
2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

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

2.9 Drug substance specification
Enalapril maleate production is controlled by certificates of suitability, which ensure compliance with the current European Pharmacopoeia.

2.10 TSE Compliance
With the exception of lactose monohydrate, no materials of animal or human origin are used in the finished products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals in the same conditions as milk for human consumption and poses no risk of BSE/TSE transmission.

3. EXPERT REPORTS
The applicant has included expert reports in Module 2 of each application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed Summaries of Product Characteristics are consistent with the details registered for the cross-reference products.

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

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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 mock-ups are comparable to the mock-ups registered for the cross-reference products and comply 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 applications are acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
For these applications, the data are consistent with that previously assessed for the cross-reference products and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Enalapril maleate is a well-known drug and has been used for many years. These applications are identical to previously granted applications for Enalapril Maleate 5, 10 and 20mg Tablets (PL 18224/0024-26), which were granted to Karib Kemi Pharma Limited on 23rd December 2004.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the product is identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

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

<table>
<thead>
<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 1&lt;sup&gt;st&lt;/sup&gt; February 2008.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 8&lt;sup&gt;th&lt;/sup&gt; February 2008.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information on 27&lt;sup&gt;th&lt;/sup&gt; March 2008, 3&lt;sup&gt;rd&lt;/sup&gt; November 2008, 15&lt;sup&gt;th&lt;/sup&gt; January 2009, 5&lt;sup&gt;th&lt;/sup&gt; February 2009 and 24&lt;sup&gt;th&lt;/sup&gt; February 2009.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 13&lt;sup&gt;th&lt;/sup&gt; October 2008, 19&lt;sup&gt;th&lt;/sup&gt; November 2008, 4&lt;sup&gt;th&lt;/sup&gt; February 2009, 11&lt;sup&gt;th&lt;/sup&gt; February 2009 and 19&lt;sup&gt;th&lt;/sup&gt; March 2009.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 5&lt;sup&gt;th&lt;/sup&gt; June 2009.</td>
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ENALAPRIL MALEATE 5MG TABLETS
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
1 NAME OF THE MEDICINAL PRODUCT
Enalapril maleate 5 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5mg of Enalapril maleate

Excipients: Each tablet contains 79.70mg of lactose monohydrate (see section 4.4)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White circular biplanar uncoated tablets with 5 embossed on one face and score line on the other. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Treatment of Hypertension
• Treatment of Symptomatic Heart Failure
• Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤ 35%)
(See Section 5.1.)

4.2 Posology and method of administration
The absorption of Enalapril 5mg tablets is not affected by food.

The dose should be individualised according to patient profile (see section 4.4) and blood pressure response.

Hypertension: The initial dose is 5 to maximally 20 mg, depending on the degree of hypertension and the condition of the patient (see below). Enalapril 5mg tablets are given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (e.g. renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 5 mg or lower is recommended in such patients and the initiation of treatment should take place under medical supervision.

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril. A starting dose of 5 mg or lower is recommended in such patients. If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalapril 5mg tablets. Renal function and serum potassium should be monitored.

The usual maintenance dose is 20 mg daily. The maximum maintenance dose is 40 mg daily.

Heart Failure/Asymptomatic Left Ventricular Dysfunction: In the management of symptomatic heart failure, Enalapril 5mg tablets are used in addition to diuretics and, where appropriate, digitalis or beta-blockers. The initial dose of Enalapril 5mg tablets in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of symptomatic hypotension following initiation of therapy with Enalapril 5mg tablets in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. This dose titration is recommended to be performed over a 2 to 4 week period. The maximum dose is 40 mg daily given in two divided doses.
Suggested Dosage Titration of Enalapril 5mg tablets in Patients with Heart Failure/Asymptomatic Left Ventricular Dysfunction:

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose mg/day</th>
</tr>
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<tbody>
<tr>
<td>Week 1</td>
<td>Days 1 to 3: 2.5 mg/day* in a single dose</td>
</tr>
<tr>
<td></td>
<td>Days 4 to 7: 5 mg/day in two divided doses</td>
</tr>
<tr>
<td>Week 2</td>
<td>10 mg/day in a single dose or in two divided doses</td>
</tr>
<tr>
<td>Weeks 3 and 4</td>
<td>20 mg/day in a single dose or in two divided doses</td>
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</table>

*Special precautions should be followed in patients with impaired renal function or taking diuretics (see section 4.4).

Blood pressure and renal function should be monitored closely both before and after starting treatment with Enalapril 5mg tablets (see section 4.4) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with Enalapril 5mg tablets. The appearance of hypotension after the initial dose of Enalapril 5mg tablets does not imply that hypotension will recur during chronic therapy with Enalapril 5mg tablets and does not preclude continued use of the drug. Serum potassium and renal function also should be monitored.

**Dosage in Renal Insufficiency:**
Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

<table>
<thead>
<tr>
<th>Creatinine Clearance (CrCL) mL/min</th>
<th>Initial Dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>30&lt;CrCL&lt;80 ml/min.</td>
<td>5 - 10 mg</td>
</tr>
<tr>
<td>10&lt;CrCL&lt;30 ml/min.</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>CrCL &lt; 10 ml/min.</td>
<td>2.5 mg on dialysis days*</td>
</tr>
</tbody>
</table>

*See section 4.4 - Haemodialysis Patients.

Enalaprilat is dialysable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

**Use in Elderly:**
The dose should be in line with the renal function of the elderly patient (see section 4.4 - Renal Function Impairment).

**Use in paediatrics:**
There is limited clinical trial experience of the use of Enalapril 5mg tablets in hypertensive paediatric patients (see sections 4.4, 5.1 and 5.2).

For patients who can swallow tablets, the dose should be individualised according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. Enalapril 5mg tablets are given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg (see section 4.4).

Enalapril 5mg tablets are not recommended in neonates and in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available.
4.3 Contraindications

- Hypersensitivity to enalapril, to any of the excipients or any other ACE inhibitor
- History of angioedema associated with previous ACE-Inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

4.4 Special warnings and precautions for use

**Pretreatment assessment of renal function:**
Evaluation of the patient should include assessment of renal function prior to initiation of therapy, and during treatment where appropriate.

**Symptomatic hypotension:**
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril maleate 5 mg tablets, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment (see section 4.2 for management of these patients). In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension develops, the patient should be placed in a supine position. Volume repletion with oral fluids or intravenous normal saline may be required. Intravenous atropine may be necessary if there is associated bradycardia. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Enalapril maleate 5 mg tablets. This effect is anticipated, and usually is not a reason to discontinue treatment. If such hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or Enalapril maleate 5 mg tablets may become necessary.

**Aortic or mitral valve 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:**
In cases of renal impairment (creatinine clearance <80 ml/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance, 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 maleate 5 mg tablets and has been occurring 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 maleate 5 mg tablets is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when Enalapril maleate 5 mg tablets have been given concurrently with a diuretic. Dosage reduction of Enalapril maleate 5 mg tablets and/or discontinuation of the diuretic may be required. This situation should raise the possibility of an underlying renal artery stenosis.
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 occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procarbamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity / Angioneurotic oedema:
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported with angiotensin-converting enzyme inhibitors, including Enalapril maleate 5 mg tablets. This may occur at any time during treatment. In such cases, Enalapril maleate 5 mg tablets should be discontinued immediately 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 angioedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction especially those with a history of airway surgery. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to 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).

Other hypersensitivity reactions including urticaria have been reported.

Anaphylactic reactions during hymenoptera desensitisation:
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom (e.g. Bee or Wasp venom) have experienced life-threatening anaphylactoid reactions. These
reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

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

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

Hypoglycaemia:
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor, should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See section 4.5 - Antidiabetics).

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 / Anesthesia:
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Enalapril maleate 5 mg tablets block angiotensin-II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (>70 years) diabetes mellitus, intercurrent events in particular dehydration, acute decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. 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 (see section 4.5).

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

Paediatric use:
There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see sections 4.2, 5.1 and 5.2) Enalapril maleate is not recommended in children in other indications than hypertension.

Enalapril maleate is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available. (see section 4.2).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative
antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

Lactose:
Enalapril maleate 5mg tablets contain lactose and therefore should not be used by patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Enalapril maleate 5mg tablets contain less than 200mg of lactose per tablet.

4.5 Interaction with other medicinal products and other forms of interaction
Combination with other antihypertensive agents such as beta-blockers, hydralazine, methyldopa, calcium antagonists, and diuretics may increase the antihypertensive efficacy. Adrenergic-blocking drugs should only be combined with Enalapril maleate 5 mg tablets under careful supervision. Concomitant propranolol may reduce the bioavailability of Enalapril maleate 5 mg tablets, but this does not appear to be of any clinical significance. Concomitant use with nitroglycerine and other nitrates, or other vasodilators may further reduce blood pressure.

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

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 maleate (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril maleate.

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 maleate 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):
When ACE inhibitors are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly.
Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

**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.

**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. Long term controlled trials with enalapril have not been confirmed these findings, and do not preclude the use of enalapril in diabetic patients. It is advised however, that caution should be exercised in this patient population.

**Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide:**
Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

**Alcohol:**
Alcohol enhances the hypotensive effect of ACE inhibitors.

**Acetyl salicylic acid, thrombolytics and β-blockers:**
Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β-blockers.

**Antacids:**
Induce decreased bioavailability of ACE inhibitors.

**Ciclosporin:**
Ciclosporin increases the risk of hyperkalaemia with ACE inhibitors.

### 4.6 Pregnancy and lactation

**Pregnancy:**

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimesters 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).
Lactation:
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 the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of Enalapril in a breastfeeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

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.

4.8 Undesirable effects
Undesirable effects reported for enalapril include:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000; very rare (< 1/10,000), not known (cannot be estimated from the available data)

Blood and the lymphatic system disorders:
Uncommon: anaemia (including aplastic and haemolytic).

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

Cardiac and vascular disorders:
Very common: dizziness.

Common: hypotension (including orthostatic hypotension), syncope, chest pain, rhythm disturbances, angina pectoris, tachycardia.

Uncommon: orthostatic hypotension, palpitations, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Rare: Raynaud's phenomenon

Eye disorders:
Very common: blurred vision.

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
General disorders and administration site conditions:
Very common: asthenia.
Common: fatigue.
Uncommon: muscle cramps, flushing, tinnitus, malaise, fever.

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

Investigations:
Common: hyperkalaemia, increases in serum creatinine.
Uncommon: increases in blood urea, hyponatraemia.
Rare: elevations of liver enzymes, elevations of serum bilirubin.

Metabolism and nutrition disorders:
Uncommon: hypoglycaemia (see section 4.4).

Nervous system and psychiatric disorders:
Common: headache, depression.
Uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo
Rare: dream abnormality, sleep disorders.

Renal and urinary disorders:
Uncommon: renal dysfunction, renal failure, proteinuria.
Rare: oliguria.

Reproductive system and breast disorders:
Uncommon: impotence.
Rare: gynecomastia.

Respiratory, thoracic and mediastinal disorders:
Very common: cough.
Common: dyspnoea.
Uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma.
Rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia.

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, a positive ANA, elevated ESR,
eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

4.9 Overdose

Limited data are available for overdosage in humans. 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-aldosterone system, and stupor. Serum enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of Enalapril, 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 sulphate). Enalaprilat may be removed from the general circulation by haemodialysis. (see section 4.4 - Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code C09AA02  Pharmacotherapeutic group: ACE inhibitors, plain

Enalapril 5mg tablets contain 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 catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolyzed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

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

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 pretreatment glomerular filtration rates, the rates were usually increased.
In short term clinical studies in diabetic and nondiabetic 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 hypokalemia.

In patients with heart failure on therapy with digoxin and diuretics, treatment with oral or Injection Enalapril was associated with decreases in peripheral resistance and blood pressure. Cardiac output increased, while heart rate (usually elevated in patients with heart failure) decreased. Pulmonary capillary wedge pressure was also reduced. Exercise tolerance and severity of heart failure, as measured by New York Heart Association criteria, improved. These actions continued during chronic therapy.

In patients with mild to moderate heart failure, enalapril retarded progressive cardiac dilatation/enlargement and failure, as evidenced by reduced left ventricular end diastolic and systolic volumes and improved ejection fraction.

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Prevention trial) examined a population with asymptomatic left ventricular dysfunction (LVEF<35%). 4228 patients were randomised to receive either placebo (n=2117) or enalapril (n=2111). In the placebo group, 818 patients had heart failure or died (38.6%) as compared with 630 in the enalapril group (29.8%) (risk reduction: 29%; 95% CI; 21 - 36%; p<0.001). 518 patients in the placebo group (24.5%) and 434 in the enalapril group (20.6%) died or were hospitalised for new or worsening heart failure (risk reduction 20%; 95% CI; 9 - 30%; p<0.001).

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Treatment trial) examined a population with symptomatic congestive heart failure due to systolic dysfunction (ejection fraction <35%). 2569 patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n=1284) or enalapril (n=1285). There were 510 deaths in the placebo group (39.7%) as compared with 452 in the enalapril group (35.2%) (reduction in risk, 16%; 95% CI, 5 - 26%; p=0.0036). There were 461 cardiovascular deaths in the placebo group as compared with 399 in the enalapril group (risk reduction 18%, 95% CI, 6 - 28%, p<0.002), mainly due to a decrease of deaths due to progressive heart failure (251 in the placebo group vs 209 in the enalapril group, risk reduction 22%, 95% CI, 6 - 35%). Fewer patients died or were hospitalised for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26%; 95% CI, 18 - 34%; p<0.0001). Overall in SOLVD study, in patients with left ventricular dysfunction, Enalapril 5mg tablets reduced the risk of myocardial infarction by 23% (95% CI, 11 – 34%; p<0.001) and reduced the risk of hospitalisation for unstable angina pectoris by 20% (95% CI, 9 – 29%; p<0.001).

There is limited experience of the use in hypertensive paediatric patients>6 years. In a clinical study involving 110 hypertensive paediatric patients 6 to 16 years of age with a body weight ≥20 kg and a glomerular filtration rate≥30 ml/min/1.73 m², patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥50 kg received either 1.25, 5 or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. The adverse experience profile for paediatric patients is not different from that seen in adult patients.
5.2 Pharmacokinetic properties

Absorption:
Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablet is approximately 60%. The absorption of oral Enalapril is not influenced by the presence of food in the gastrointestinal tract. Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril tablet. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were reached after 4 days of treatment.

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

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

Children and adolescents:
A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to 16 years following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. There were no major differences in the pharmacokinetics of enalaprilat in children compared with historic data in adults. The data indicate an increase in AUC (normalised to dose per body weight) with increased age; however, an increase in AUC is not observed when data are normalised by body surface area. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours.

Lactation:
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7µg/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively 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 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.
**5.3 Preclinical safety data**

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.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Enalapril maleate 5 mg tablets contain the following inactive ingredients:
- Lactose monohydrate
- Maize starch
- Glycerol Distearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

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

**6.5 Nature and contents of container**

PVC/Aluminium foil blisters containing 28 tablets.

**6.6 Special precautions for disposal**

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHENTICATION HOLDER**

Medreich plc
9 Royal Parade
Kew Gardens
Surrey TW9 3QD
United Kingdom

**8 MARKETING AUTHENTICATION NUMBER(S)**

PL 21880/0003

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

05/06/2009

**10 DATE OF REVISION OF THE TEXT**

05/06/2009
1 NAME OF THE MEDICINAL PRODUCT
Enalapril maleate 10 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10mg of Enalapril maleate

Excipients: Each tablet contains 98.30mg of lactose monohydrate (see section 4.4)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

White circular biplanar uncoated tablets with 10 embossed on one face and score line on the other. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
• Treatment of Hypertension
• Treatment of Symptomatic Heart Failure
• Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤ 35%)
(See Section 5.1.)

4.2 Posology and method of administration
The absorption of Enalapril 10mg tablets is not affected by food.

The dose should be individualised according to patient profile (see section 4.4) and blood pressure response.

Hypertension:
The initial dose is 5 to maximally 20 mg, depending on the degree of hypertension and the condition of the patient (see below). Enalapril 10mg tablets are given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (e.g. renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 5 mg or lower is recommended in such patients and the initiation of treatment should take place under medical supervision.

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril. A starting dose of 5 mg or lower is recommended in such patients. If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalapril 10mg tablets. Renal function and serum potassium should be monitored.

The usual maintenance dose is 20 mg daily. The maximum maintenance dose is 40 mg daily.

Heart Failure/Asymptomatic Left Ventricular Dysfunction:
In the management of symptomatic heart failure, Enalapril 10mg tablets are used in addition to diuretics and, where appropriate, digitalis or beta-blockers. The initial dose of Enalapril 10mg tablets in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of symptomatic hypotension following initiation of therapy with Enalapril 10mg tablets in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. This dose titration is recommended to be performed over a 2 to 4 week period. The maximum dose is 40 mg daily given in two divided doses.
Suggested Dosage Titration of Enalapril 10mg tablets in Patients with Heart Failure/Asymptomatic Left Ventricular Dysfunction:

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Days 1 to 3: 2.5 mg/day* in a single dose</td>
</tr>
<tr>
<td></td>
<td>Days 4 to 7: 5 mg/day in two divided doses</td>
</tr>
<tr>
<td>Week 2</td>
<td>10 mg/day in a single dose or in two divided doses</td>
</tr>
<tr>
<td>Weeks 3 and 4</td>
<td>20 mg/day in a single dose or in two divided doses</td>
</tr>
</tbody>
</table>

*Special precautions should be followed in patients with impaired renal function or taking diuretics (see section 4.4).

Blood pressure and renal function should be monitored closely both before and after starting treatment with Enalapril 10mg tablets (see section 4.4) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with Enalapril 10mg tablets. The appearance of hypotension after the initial dose of Enalapril 10mg tablets does not imply that hypotension will recur during chronic therapy with Enalapril 10mg tablets and does not preclude continued use of the drug. Serum potassium and renal function also should be monitored.

**Dosage in Renal Insufficiency:**

Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

<table>
<thead>
<tr>
<th>Creatinine Clearance (CrCL) mL/min</th>
<th>Initial Dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>30&lt;CrCL&lt;80 ml/min.</td>
<td>5 - 10 mg</td>
</tr>
<tr>
<td>10&lt;CrCL&lt;30 ml/min.</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>CrCL&lt;10 ml/min.</td>
<td>2.5 mg on dialysis days*</td>
</tr>
</tbody>
</table>

*See section 4.4 - Haemodialysis Patients.

Enalaprilat is dialysable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

**Use in Elderly:**
The dose should be in line with the renal function of the elderly patient (see section 4.4 - Renal Function Impairment).

**Use in paediatrics:**
There is limited clinical trial experience of the use of Enalapril 10mg tablets in hypertensive paediatric patients (see sections 4.4, 5.1 and 5.2).

For patients who can swallow tablets, the dose should be individualised according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. Enalapril 10mg tablets are given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg (see section 4.4).

Enalapril 10mg tablets are not recommended in neonates and in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available.
4.3 Contraindications
- Hypersensitivity to enalapril, to any of the excipients or any other ACE inhibitor
- History of angioedema associated with previous ACE-Inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

4.4 Special warnings and precautions for use
Pretreatment assessment of renal function:
Evaluation of the patient should include assessment of renal function prior to initiation of therapy, and during treatment where appropriate.

Symptomatic hypotension:
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril maleate 10mg tablets, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment (see section 4.2 for management of these patients). In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension develops, the patient should be placed in a supine position. Volume repletion with oral fluids or intravenous normal saline may be required. Intravenous atropine may be necessary if there is associated bradycardia. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Enalapril maleate 10mg tablets. This effect is anticipated, and usually is not a reason to discontinue treatment. If such hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or Enalapril maleate 10mg tablets may become necessary.

Aortic or mitral valve 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:
In cases of renal impairment (creatinine clearance <80 ml/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance, 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 maleate 10mg tablets and has been occurring 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 maleate 10mg tablets is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when Enalapril maleate 10mg tablets have been given concurrently with a diuretic. Dosage reduction of Enalapril maleate 10mg tablets and/or discontinuation of the diuretic may be required. This situation should raise the possibility of an underlying renal artery stenosis.
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 occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procarbazine, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity / Angioneurotic oedema:
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported with angiotensin-converting enzyme inhibitors, including Enalapril maleate 10mg tablets. This may occur at any time during treatment. In such cases, Enalapril maleate 10mg tablets should be discontinued immediately and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient.

Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

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

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to 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).

Other hypersensitivity reactions including urticaria have been reported.

Anaphylactic reactions during hymenoptera desensitisation:
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom (e.g. Bee or Wasp venom) have experienced life-threatening anaphylactoid reactions. These
reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.

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

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

**Hypoglycaemia:**
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor, should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See section 4.5 - Antidiabetics).

**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 / Anesthesia:**
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Enalapril maleate 10mg tablets block angiotensin-II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

**Hyperkalaemia:**
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years) diabetes mellitus, inter-current events in particular dehydration, acute decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. 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 (see section 4.5).

**Lithium:**
The combination of lithium and enalapril is generally not recommended (see section 4.5).

**Paediatric use:**
There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see sections 4.2, 5.1 and 5.2) Enalapril maleate is not recommended in children in other indications than hypertension.

Enalapril maleate is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available. (see section 4.2).

**Pregnancy:**
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative
antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

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

Lactose:
Enalapril maleate 10mg tablets contain lactose and therefore should not be used by patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Enalapril maleate 10mg tablets contain less than 200mg of lactose per tablet.

4.5 Interaction with other medicinal products and other forms of interaction
Combination with other antihypertensive agents such as beta-blockers, hydralazine, methyldopa, calcium antagonists, and diuretics may increase the antihypertensive efficacy. Adrenergic-blocking drugs should only be combined with Enalapril maleate 10mg tablets under careful supervision. Concomitant propranolol may reduce the bioavailability of Enalapril maleate 10mg tablets, but this does not appear to be of any clinical significance. Concomitant use with nitroglycerine and other nitrates, or other vasodilators may further reduce blood pressure.

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

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 maleate (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril maleate.

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 maleate 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):
When ACE inhibitors are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly.
Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

**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.

**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. Long term controlled trials with enalapril have not been confirmed these findings, and do not preclude the use of enalapril in diabetic patients. It is advised however, that caution should be exercised in this patient population.

**Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide:**
Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

**Alcohol:**
Alcohol enhances the hypotensive effect of ACE inhibitors.

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

**Antacids:**
Induce decreased bioavailability of ACE inhibitors.

**Ciclosporin:**
Ciclosporin increases the risk of hyperkalaemia with ACE inhibitors.

### 4.6 Pregnancy and lactation

**Pregnancy:**

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).
Lactation:
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 the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of Enalapril 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.

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.

4.8 Undesirable effects
Undesirable effects reported for enalapril include:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000; very rare (< 1/10,000), not known (cannot be estimated from the available data)

Blood and the lymphatic system disorders:
Uncommon: anaemia (including aplastic and haemolytic).

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

Cardiac and vascular disorders:
Very common: hypotension (including orthostatic hypotension), syncope, chest pain, rhythm disturbances, angina pectoris, tachycardia.

Uncommon: orthostatic hypotension, palpitations, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Rare: Raynaud's phenomenon

Eye disorders:
Very common: blurred vision.

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
General disorders and administration site conditions:
Very common: asthenia.

Common: fatigue.

Uncommon: muscle cramps, flushing, tinnitus, malaise, fever.

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

Investigations:
Common: hyperkalaemia, increases in serum creatinine.

Uncommon: increases in blood urea, hyponatraemia.

Rare: elevations of liver enzymes, elevations of serum bilirubin.

Metabolism and nutrition disorders:
Uncommon: hypoglycaemia (see section 4.4).

Nervous system and psychiatric disorders:
Common: headache, depression.

Uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo

Rare: dream abnormality, sleep disorders.

Renal and urinary disorders:
Uncommon: renal dysfunction, renal failure, proteinuria.

Rare: oliguria.

Reproductive system and breast disorders:
Uncommon: impotence.

Rare: gynecomastia.

Respiratory, thoracic and mediastinal disorders:
Very common: cough.

Common: dyspnoea.

Uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma.

Rare: pulmonary infiltrates, rhinitis, allergic alveolitis eosinophilic pneumonia.

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, a positive ANA, elevated ESR,
eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

4.9 Overdose
Limited data are available for overdosage in humans. 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-aldosterone system, and stupor. Serum enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of Enalapril, 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 sulphate). Enalaprilat may be removed from the general circulation by haemodialysis. (see section 4.4 - Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Enalapril 10mg tablets contain 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 catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolyzed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

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

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 pretreatment glomerular filtration rates, the rates were usually increased.
In short term clinical studies in diabetic and nondiabetic 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 hypokalemia.

In patients with heart failure on therapy with digitalis and diuretics, treatment with oral or Injection Enalapril was associated with decreases in peripheral resistance and blood pressure. Cardiac output increased, while heart rate (usually elevated in patients with heart failure) decreased. Pulmonary capillary wedge pressure was also reduced. Exercise tolerance and severity of heart failure, as measured by New York Heart Association criteria, improved. These actions continued during chronic therapy.

In patients with mild to moderate heart failure, enalapril retarded progressive cardiac dilatation/enlargement and failure, as evidenced by reduced left ventricular end diastolic and systolic volumes and improved ejection fraction.

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Prevention trial) examined a population with asymptomatic left ventricular dysfunction (LVEF<35%). 4228 patients were randomised to receive either placebo (n=2117) or enalapril (n=2111). In the placebo group, 818 patients had heart failure or died (38.6%) as compared with 630 in the enalapril group (29.8%) (risk reduction: 29%; 95% CI; 21 - 36%; p<0.001). 518 patients in the placebo group (24.5%) and 434 in the enalapril group (20.6%) died or were hospitalised for new or worsening heart failure (risk reduction 20%; 95% CI; 9 - 30%; p<0.001).

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Treatment trial) examined a population with symptomatic congestive heart failure due to systolic dysfunction (ejection fraction <35%). 2569 patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n=1284) or enalapril (n=1285). There were 510 deaths in the placebo group (39.7%) as compared with 452 in the enalapril group (35.2%) (reduction in risk, 16%; 95% CI, 5 - 26%; p=0.0036). There were 461 cardiovascular deaths in the placebo group as compared with 399 in the enalapril group (risk reduction 18%, 95% CI, 6 - 28%, p<0.002), mainly due to a decrease of deaths due to progressive heart failure (251 in the placebo group vs 209 in the enalapril group, risk reduction 22%, 95% CI, 6 - 35%). Fewer patients died or were hospitalised for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26%; 95% CI; 18 - 34%; p<0.0001). Overall in SOLVD study, in patients with left ventricular dysfunction, Enalapril 10mg tablets reduced the risk of myocardial infarction by 23% (95% CI, 11 – 34%; p<0.001) and reduced the risk of hospitalisation for unstable angina pectoris by 20% (95% CI, 9 – 29%; p<0.001).

There is limited experience of the use in hypertensive paediatric patients>6 years. In a clinical study involving 110 hypertensive paediatric patients 6 to 16 years of age with a body weight ≥20 kg and a glomerular filtration rate>30 ml/min/1.73 m², patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥50 kg received either 1.25, 5 or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. The adverse experience profile for paediatric patients is not different from that seen in adult patients.
### 5.2 Pharmacokinetic properties

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

Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril tablet. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were reached after 4 days of treatment.

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

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

**Children and adolescents:**
A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to 16 years following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. There were no major differences in the pharmacokinetics of enalaprilat in children compared with historic data in adults. The data indicate an increase in AUC (normalised to dose per body weight) with increased age; however, an increase in AUC is not observed when data are normalised by body surface area. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours.

**Lactation:**
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7μg/L (range 0.54 to 5.9 μg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7μg/L (range 1.2 to 2.3μg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively 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 hour period was 1.44μg/L and 0.63 μg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2μg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.
5.3 Preclinical safety data
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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Enalapril maleate 10mg tablets contain the following inactive ingredients:
Lactose monohydrate
Maize starch
Glycerol Distearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
PVC/Aluminium foil blisters containing 28 tablets.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Medreich plc
9 Royal Parade
Kew Gardens
Surrey TW9 3QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 21880/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/06/2009

10 DATE OF REVISION OF THE TEXT
05/06/2009
1 **NAME OF THE MEDICINAL PRODUCT**  
Enalapril maleate 20mg Tablets.

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**  
Each tablet contains 20mg of Enalapril maleate  
Excipients: Each tablet contains 111.00mg of lactose monohydrate (see section 4.4)  
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**  
Tablet.  
White circular biplanar uncoated tablets with 20 embossed on one face and score line on the other. The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 **CLINICAL PARTICULARS**  
4.1 **Therapeutic indications**  
• Treatment of Hypertension  
• Treatment of Symptomatic Heart Failure  
• Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤ 35%)  
(See Section 5.1.)

4.2 **Posology and method of administration**  
The absorption of Enalapril 20mg tablets is not affected by food.  
The dose should be individualised according to patient profile (see section 4.4) and blood pressure response.  

**Hypertension:**  
The initial dose is 5 to maximally 20 mg, depending on the degree of hypertension and the condition of the patient (see below). Enalapril 20mg tablets are given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (e.g. renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 5 mg or lower is recommended in such patients and the initiation of treatment should take place under medical supervision.  
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril. A starting dose of 5 mg or lower is recommended in such patients. If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalapril 20mg tablets. Renal function and serum potassium should be monitored.  
The usual maintenance dose is 20 mg daily. The maximum maintenance dose is 40 mg daily.

**Heart Failure/Asymptomatic Left Ventricular Dysfunction:**  
In the management of symptomatic heart failure, Enalapril 20mg tablets are used in addition to diuretics and, where appropriate, digitalis or beta-blockers. The initial dose of Enalapril 20mg tablets in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of symptomatic hypotension following initiation of therapy with Enalapril 20mg tablets in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. This dose titration is recommended to be performed over a 2 to 4 week period. The maximum dose is 40 mg daily given in two divided doses.
Suggested Dosage Titration of Enalapril 20mg tablets in Patients with Heart Failure/Asymptomatic Left Ventricular Dysfunction:

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose mg/day</th>
</tr>
</thead>
</table>
| Week 1 | Days 1 to 3: 2.5 mg/day* in a single dose  
Days 4 to 7: 5 mg/day in two divided doses |
| Week 2 | 10 mg/day in a single dose or in two divided doses |
| Weeks 3 and 4 | 20 mg/day in a single dose or in two divided doses |

*Special precautions should be followed in patients with impaired renal function or taking diuretics (see section 4.4).

Blood pressure and renal function should be monitored closely both before and after starting treatment with Enalapril 20mg tablets (see section 4.4) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with Enalapril 20mg tablets. The appearance of hypotension after the initial dose of Enalapril 20mg tablets does not imply that hypotension will recur during chronic therapy with Enalapril 20mg tablets and does not preclude continued use of the drug. Serum potassium and renal function also should be monitored.

**Dosage in Renal Insufficiency:**
Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

<table>
<thead>
<tr>
<th>Creatinine Clearance (CrCL ml/min)</th>
<th>Initial Dose mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>30&lt;CrCL&lt;80 ml/min.</td>
<td>5 - 10 mg</td>
</tr>
<tr>
<td>10&lt;CrCL &lt; 30 ml/min.</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>CrCL &lt; 10 ml/min.</td>
<td>2.5 mg on dialysis days*</td>
</tr>
</tbody>
</table>

*See section 4.4 - Haemodialysis Patients.

Enalaprilat is dialysable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

**Use in Elderly:**
The dose should be in line with the renal function of the elderly patient (see section 4.4 - Renal Function Impairment).

**Use in paediatrics:**
There is limited clinical trial experience of the use of Enalapril 20mg tablets in hypertensive paediatric patients (see sections 4.4, 5.1 and 5.2).

For patients who can swallow tablets, the dose should be individualised according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients $\geq$ 50 kg. Enalapril 20mg tablets are given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients $\geq$ 50 kg (see section 4.4).

Enalapril 20mg tablets are not recommended in neonates and in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available.
4.3 Contraindications

- Hypersensitivity to enalapril, to any of the excipients or any other ACE inhibitor
- History of angioedema associated with previous ACE-Inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)

4.4 Special warnings and precautions for use

Pretreatment assessment of renal function:
Evaluation of the patient should include assessment of renal function prior to initiation of therapy, and during treatment where appropriate.

Symptomatic hypotension:
Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril maleate 20 mg tablets, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment (see section 4.2 for management of these patients). In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of enalapril and/or diuretic is adjusted.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension develops, the patient should be placed in a supine position. Volume repletion with oral fluids or intravenous normal saline may be required. Intravenous atropine may be necessary if there is associated bradycardia. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Enalapril maleate 20 mg tablets. This effect is anticipated, and usually is not a reason to discontinue treatment. If such hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or Enalapril maleate 20 mg tablets may become necessary.

Aortic or mitral valve 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:
In cases of renal impairment (creatinine clearance <80 ml/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance, 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 maleate 20 mg tablets and has been occurring 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 maleate 20 mg tablets is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease, have developed increases in blood urea and creatinine when Enalapril maleate 20 mg tablets have been given concurrently with a diuretic. Dosage reduction of Enalapril maleate 20 mg tablets and/or discontinuation of the diuretic may be required. This situation should raise the possibility of an underlying renal artery stenosis.
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 occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity / Angioneurotic oedema:
Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported with angiotensin-converting enzyme inhibitors, including Enalapril maleate 20 mg tablets. This may occur at any time during treatment. In such cases, Enalapril maleate 20 mg tablets should be discontinued immediately and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient.

Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

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

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to 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).

Other hypersensitivity reactions including urticaria have been reported.

Anaphylactic reactions during hymenoptera desensitisation:
Rarely, patients receiving ACE inhibitors during desensitisation with hymenoptera venom (e.g. Bee or Wasp venom) have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitisation.
Anaphylactoid reactions during LDL apheresis:
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

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

Hypoglycaemia:
Diabetic patients treated with oral antidiabetic agents or insulin starting an ACE inhibitor, should be told to closely monitor for hypoglycemia, especially during the first month of combined use. (See section 4.5 - Antidiabetics).

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 / Anesthesia:
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Enalapril maleate 20 mg tablets block angiotensin-II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including enalapril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (>70 years) diabetes mellitus, intercurrent events in particular dehydration, acute decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. 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 (see section 4.5).

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

Paediatric use:
There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see sections 4.2, 5.1 and 5.2) Enalapril maleate is not recommended in children in other indications than hypertension.

Enalapril maleate is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available. (see section 4.2).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
Ethnic differences:
As with other angiotensin-converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Lactose:
Enalapril maleate 20mg tablets contain lactose and therefore should not be used by patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Enalapril maleate 20mg tablets contain less than 200mg of lactose per tablet.

4.5 Interaction with other medicinal products and other forms of interaction
Combination with other antihypertensive agents such as beta-blockers, hydralazine, methyldopa, calcium antagonists, and diuretics may increase the antihypertensive efficacy. Adrenergic-blocking drugs should only be combined with Enalapril maleate 20 mg tablets under careful supervision. Concomitant propranolol may reduce the bioavailability of Enalapril maleate 20 mg tablets, but this does not appear to be of any clinical significance. Concomitant use with nitroglycerine and other nitrates, or other vasodilators may further reduce blood pressure.

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

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 maleate (see section 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril maleate.

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 maleate 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):
When ACE inhibitors are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

Concomitant use of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly.

Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
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.

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. Long term controlled trials with enalapril have not been confirmed these findings, and do not preclude the use of enalapril in diabetic patients. It is advised however, that caution should be exercised in this patient population.

Allopurinol, cytostatic or immunosuppressive agents, systematic corticosteroids or procainamide:
Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

Alcohol:
Alcohol enhances the hypotensive effect of ACE inhibitors.

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

Antacids:
Induce decreased bioavailability of ACE inhibitors.

Ciclosporin:
Ciclosporin increases the risk of hyperkalaemia with ACE inhibitors.

4.6 Pregnancy and lactation

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimesters 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).
Lactation:
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 the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In the case of an older infant, the use of Enalapril 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.

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.

4.8 Undesirable effects
Undesirable effects reported for enalapril include:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000; very rare (< 1/10,000), not known (cannot be estimated from the available data)

Blood and the lymphatic system disorders:
Uncommon: anaemia (including aplastic and haemolytic).

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

Cardiac and vascular disorders:
Very common: dizziness.

Common: hypotension (including orthostatic hypotension), syncope, chest pain, rhythm disturbances, angina pectoris, tachycardia.

Uncommon: orthostatic hypotension, palpitations, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).

Rare: Raynaud's phenomenon

Eye disorders:
Very common: blurred vision.

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
General disorders and administration site conditions:
Very common: asthenia.

Common: fatigue.

Uncommon: muscle cramps, flushing, tinnitus, malaise, fever.

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

Investigations:
Common: hyperkalaemia, increases in serum creatinine.

Uncommon: increases in blood urea, hyponatraemia.

Rare: elevations of liver enzymes, elevations of serum bilirubin.

Metabolism and nutrition disorders:
Uncommon: hypoglycaemia (see section 4.4).

Nervous system and psychiatric disorders:
Common: headache, depression.

Uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo

Rare: dream abnormality, sleep disorders.

Renal and urinary disorders:
Uncommon: renal dysfunction, renal failure, proteinuria.

Rare: oliguria.

Reproductive system and breast disorders:
Uncommon: impotence.

Rare: gynecomastia.

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.

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, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.
4.9 Overdose
Limited data are available for overdosage in humans. 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-aldosterone system, and stupor. Serum enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of Enalapril, 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 sulphate). Enalaprilat may be removed from the general circulation by haemodialysis. (see section 4.4 - Haemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC Code C09AA02 Pharmacotherapeutic group: ACE inhibitors, plain

Enalapril 20mg tablets contain 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 catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolyzed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

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

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 pretreatment glomerular filtration rates, the rates were usually increased.

In short term clinical studies in diabetic and nondiabetic 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 hypokalemia.

In patients with heart failure on therapy with digitalis and diuretics, treatment with oral or Injection Enalapril was associated with decreases in peripheral resistance and blood pressure. Cardiac output increased, while heart rate (usually elevated in patients with heart failure) decreased. Pulmonary capillary wedge pressure was also reduced. Exercise tolerance and severity of heart failure, as measured by New York Heart Association criteria, improved. These actions continued during chronic therapy.

In patients with mild to moderate heart failure, enalapril retarded progressive cardiac dilatation/enlargement and failure, as evidenced by reduced left ventricular end diastolic and systolic volumes and improved ejection fraction.

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Prevention trial) examined a population with asymptomatic left ventricular dysfunction (LVEF<35%). 4228 patients were randomised to receive either placebo (n=2117) or enalapril (n=2111). In the placebo group, 818 patients had heart failure or died (38.6%) as compared with 630 in the enalapril group (29.8%) (risk reduction: 29%; 95% CI, 21 - 36%; p=0.001). 518 patients in the placebo group (24.5%) and 434 in the enalapril group (20.6%) died or were hospitalised for new or worsening heart failure (risk reduction 20%; 95% CI, 9 - 30%; p<0.001).

A multicentre, randomised, double-blind, placebo-controlled trial (SOLVD Treatment trial) examined a population with symptomatic congestive heart failure due to systolic dysfunction (ejection fraction <35%). 2569 patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n=1284) or enalapril (n=1285). There were 510 deaths in the placebo group (39.7%) as compared with 452 in the enalapril group (35.2%) (reduction in risk, 16%; 95% CI, 5 - 26%; p=0.0036). There were 461 cardiovascular deaths in the placebo group as compared with 399 in the enalapril group (risk reduction 18%, 95% CI, 6 - 28%, p<0.002), mainly due to a decrease of deaths due to progressive heart failure (251 in the placebo group vs 209 in the enalapril group, risk reduction 22%, 95% CI, 6 - 35%). Fewer patients died or were hospitalised for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26%; 95% CI, 18 - 34%; p=0.0001). Overall in SOLVD study, in patients with left ventricular dysfunction, Enalapril 20mg tablets reduced the risk of myocardial infarction by 23% (95% CI, 11 – 34%; p<0.001) and reduced the risk of hospitalisation for unstable angina pectoris by 20% (95% CI, 9 – 29%; p<0.001).

There is limited experience of the use in hypertensive paediatric patients>6 years. In a clinical study involving 110 hypertensive paediatric patients 6 to 16 years of age with a body weight ≥20 kg and a glomerular filtration rate>30 ml/min/1.73 m², patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥50 kg received either 1.25, 5 or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. The adverse experience profile for paediatric patients is not different from that seen in adult patients.

5.2 Pharmacokinetic properties

Absorption:
Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablet is approximately 60%. The absorption of oral Enalapril is not influenced by the presence of food in the gastrointestinal tract.
Following absorption, oral enalapril is rapidly and extensively hydrolysed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril tablet. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects
with normal renal function, steady-state serum concentrations of enalaprilat were reached after 4 days of treatment.

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

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

**Children and adolescents:**
A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to ≤ 16 years following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. There were no major differences in the pharmacokinetics of enalaprilat in children compared with historic data in adults. The data indicate an increase in AUC (normalised to dose per body weight) with increased age; however, an increase in AUC is not observed when data are normalised by body surface area. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours.

**Lactation:**
After a single 20 mg oral dose in five postpartum women, the average peak enalapril milk level was 1.7µg/L (range 0.54 to 5.9 µg/L) at 4 to 6 hours after the dose. The average peak enalaprilat level was 1.7µg/L (range 1.2 to 2.3µg/L); peaks occurred at various times over the 24-hour period. Using the peak milk level data, the estimated maximum intake of an exclusively 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 hour period was 1.44µg/L and 0.63 µg/L of milk respectively. Enalaprilat milk levels were undetectable (<0.2µg/L) 4 hours after a single dose of enalapril 5 mg in one mother and 10mg in two mothers; enalapril levels were not determined.

**5.3 Preclinical safety data**
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.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Enalapril maleate 20mg tablets contain the following inactive ingredients:
Lactose monohydrate
Maize starch
Glycerol Distearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
PVC/Aluminium foil blisters containing 28 tablets.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
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Surrey TW9 3QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
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ENALAPRIL Maleate 5/10/20 mg Tablets

In this leaflet:
1. What Enalapril Maleate 5, 10 and 20 mg Tablets (referred to as Enalapril Tablets in this leaflet) are and what they are used for
2. Before you take Enalapril Tablets
3. How to take Enalapril Tablets
4. Possible side effects
5. How to store Enalapril Tablets
6. Further information

1. WHAT ENALAPRIL MALEATE TABLETS ARE AND WHAT THEY ARE USED FOR

Enalapril Tablets belong to a group of medicines known as ‘ACE inhibitors’ (drug that is used to lower blood pressure). These medicines work by widening your blood vessels to make it easier for the heart to pump blood through them to all parts of your body. Your doctor has probably prescribed Enalapril Tablets for one of the following reasons:

• Your blood pressure is too high.
• You have a heart condition sometimes referred to as ‘heart failure’. This means that your heart is not working as well as it used to, in order to pump blood around your body, leading to tiredness after light exercise, breathlessness and swelling of your ankles and legs. Enalapril tablets may help treat these symptoms.
• In many patients, with a damaged heart muscle, but who have no symptoms Enalapril Tablets may help to prevent the appearance of symptoms such as shortness of breath and swelling.

2. BEFORE YOU TAKE ENALAPRIL TABLETS

Do not take Enalapril Tablets if you:
• are more than 3 months pregnant. (It is also better to avoid Enalapril Tablets in early pregnancy - see pregnancy section).
• have suffered from a reaction to Enalapril or similar medicines (i.e. ACE inhibitors) in the past, or to any of the ingredients in the past.
• have experienced the following types of reactions even if the cause is unknown: itching, nettle rash, wheezing or swelling of the hands, throat, mouth or eye lids.

If you think any of these apply to you, talk to your doctor.

Take special care with Enalapril Tablets

You must tell your doctor if you think you are (or might become) pregnant. Enalapril Tablets are 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).
Pregnancy and breast feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Enalapril Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Enalapril tablets. Enalapril tablets are 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 breast-feeding or about to start breast-feeding. Breast-feeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking Enalapril Tablets.

In the case of an older baby your doctor should advise you on the benefits and risks of taking Enalapril Tablets whilst breast-feeding, compared with other treatments.

Please speak to your doctor before taking Enalapril Tablets if any of the following apply to you.

- have kidney disease, are a dialysis patient, are taking diuretics (water tablets), are on a salt restriction diet, or have suffered from excessive vomiting or diarrhoea.
- have a heart condition called ‘aortic stenosis’ (narrowing or obstruction of the heart’s aortic valve), ‘hypertrophic cardiomyopathy’ (damaged heart muscle) or ‘outflow obstruction’.
- have had a recent kidney transplantation.
- have collagen vascular disease, are taking immunosuppressant therapy (used for the treatment of autoimmune disorders such as rheumatoid arthritis or following transplant surgery), are taking allopurinol, (used for the treatment of gout), or are taking procainamide, (used to treat abnormal heart rhythms).
- develop an infection (symptoms may be high temperature, feverish)
- have a history of angioedema (symptoms such as itching, nettle rash, wheezing or swelling of the hands, throat, mouth or eyelids) while taking other medicines.
- have diabetes and are taking antidiabetic agents or insulin to control your diabetes; you should closely monitor for low blood glucose levels especially during the first month of treatment.
- are taking potassium supplements or potassium containing salt substitutes.
- are taking lithium, used for the treatment of some psychiatric illnesses.
- have been told by your doctor that you have an intolerance to some sugars.

Please let your doctor know immediately if you develop any of the following symptoms while taking Enalapril Tablets

- jaundice (yellowing of the skin and whites of the eyes)
- a dry cough which is persistent for a long time
If you are about to undergo any of the below mentioned procedures, please tell the doctor who is treating you that you are taking Enalapril Tablets.

- a treatment called LDL apheresis, which is removal of cholesterol from your blood by a machine.
- desensitisation treatment, that is treatment to reduce the effect of an allergy to bee or wasp stings.
- any surgery or receive anaesthetics (even at the dentist).

Taking other medicines

Before starting your treatment, you should always inform your doctor about all medicines you are taking or plan to take, including those obtained without a prescription.

If you are taking any of the following medicines, you should talk to your doctor before you first start taking Enalapril Tablets.

- Potassium sparing diuretics such as spironolactone, eplerenone, triamterene or amiloride; potassium supplements, or potassium-containing salt substitutes. Enalapril Tablets may increase the levels of potassium in your blood leading to hyperkalaemia (serum or plasma levels of potassium ions above normal range). Use of these type of medicines in patients with kidney problems may lead to a significant increase in potassium in the blood which can cause serious side effects.
- Diuretics such as thiazides, loop diuretics such as furosemide, bumetanide, other antihypertensive agents and nitroglycerine, other nitrates, and other vasodilators; concomitant use with Enalapril Tablets may cause hypotension (low blood pressure).
- Tricyclic antidepressants such as amitriptyline (used for treating depression), antipsychotics such as phenothiazine derivatives (for alleviating severe anxiety), narcotics such as morphine (used to treat moderate and severe pain), or anaesthetics. Additional lowering of your blood pressure may be seen when these drugs are taken with Enalapril Tablets.

- Medicines used to relieve pain, stiffness and inflammation associated with painful conditions, particularly those affecting the muscles, bones and joints. Including gold therapy which can lead to flushing of the face, nausea, vomiting and low blood pressure when taken with ACE inhibitors including Enalapril Tablets, and non-steroidal anti-inflammatory drugs (NSAIDs) such as diflunisal or diclofenac which when taken with Enalapril Tablets may prevent your blood pressure from being well controlled and may increase the level of potassium in your blood.
- Sympathomimetics, drugs such as ephedrine, noradrenaline or adrenaline used for the treatment of hypotension, shock, cardiac failure, asthma or allergies. Taken with Enalapril Tablets these drugs may keep your blood pressure elevated.
- Antidiabetic agents such as insulin, used to lower blood sugar levels. Enalapril Tablets may cause your blood sugar levels to drop even further when taken with antidiabetic drugs.

Driving and using machines

Individual responses to medication may vary. Certain side effects like dizziness or weariness may affect some patients' ability to drive or operate machine.
Important information about some of the ingredients of Enalapril Tablets

Enalapril Tablets contain Lactose. If your doctor has told you that you have intolerance to some sugars, contact your doctor before taking this medicine. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

3. HOW TO TAKE ENALAPRIL TABLETS

Always take Enalapril Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Do not stop taking Enalapril Tablets without consulting the doctor.

You can swallow your tablets with or without food. Most people take Enalapril tablets with water.

However, if you drink alcohol while taking Enalapril Tablets, it may cause your blood pressure to drop and you may experience dizziness, light-headedness or faintness. You should also keep your alcohol intake to a minimum.

The dose you take will depend on your condition and whether you are taking any other treatment. The usual dose is:

**High blood pressure:** Initial dose is 5 mg per day, and increased gradually up to 10-20 mg per day. The maximum dose is 40 mg a day. Some patients may start on a lower dose of 2.5 mg once a day.

**Heart disorders:** In patients with heart problem, Enalapril tablets are used in addition to diuretics and where appropriate with digitalis (a drug used in congestive heart failure or for an erratic heartbeat) or beta-blockers (drugs used to treat high blood pressure and heart problems). The usual recommended starting dose is 2.5 mg a day, which is gradually increased up to 20 mg a day, given either once daily or in 2 divided doses, over a 2 to 4 week period. The maximum dose is 40 mg daily given in two divided doses.

**Reduced Renal Function:** In patients with kidney problems, your dose of Enalapril tablets will need to be adjusted depending on how well your kidneys are functioning. Kidney function is calculated by measuring the amount of creatinine (a waste product) in your urine and also by taking a blood test.

If you are having dialysis, your dosage will vary daily. Your doctor will let you know what your dose should be.

**Elderly Patients**

Your dose will be decided by your doctor, and will be based on how well your kidneys are functioning.

**Children**

Experience in the use of Enalapril tablets in children with high blood pressure is limited. If the child can swallow tablets the dose will be determined based on the child’s weight and blood pressure response. The recommended starting dose is 2.5 mg in children 20 to less than 50 kg and 5 mg in children 50 kg and over. Enalapril Tablets are given once daily. The dosage should be adjusted according to the needs of the child to a maximum of 20 mg daily in children 20 to less than 50 kg and 40 mg in children 50 kg and over.
Babies and children with kidney problems:
Enalapril tablets should not be used in babies or children with kidney problems.

If you take more Enalapril Tablets than you should
If you take too many tablets by mistake contact your doctor IMMEDIATELY.
The most common signs and symptoms of overdose are fall in blood pressure and stupor (a state of almost complete lack of consciousness). Other symptoms may include dizziness or light-headedness due to a fall in blood pressure, forceful and rapid heartbeat, rapid pulse, anxiety, cough, kidney failure, and rapid breathing.

If you forget to take Enalapril Tablets
If you miss a dose just carry on with the next one as normal, but make sure you tell your doctor. Do not take an extra one to make up.

If you stop taking Enalapril Tablets
If you stop taking your medication, your blood pressure may increase. If your blood pressure becomes too high it may affect the function of your heart and kidneys. Your doctor will tell you when you should stop taking Enalapril Tablets. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Enalapril Tablets may occasionally cause side effects in some patients.
It is very important that you stop taking Enalapril Tablets immediately and see your doctor if you have severe dizziness, light-headedness, especially at the start of treatment or when the dose is increased or when you stand up. It is vital to stop taking Enalapril Tablets and seek medical attention immediately if you begin to itch, get short of breath or wheezy and develop swelling of the hands, mouth, throat, face or eyes. Below is the list of side effects that have occurred in patients taking Enalapril Tablets.

Blood and Lymphatic system disorders
Uncommon:
• Anaemia (decrease in Red blood cells)
Rare:
• blood disorders which affect the cells or elements in the blood and are usually diagnosed by blood tests (symptoms may be tiredness, weakness, shortness of breath, inability to exercise, feeling run down, having constant or re-occurring colds, prolonged bleeding, bruising where cause is unknown)

Metabolism and nutrition disorders
Uncommon:
• Hypoglycaemia (low blood glucose level)

Nervous system and psychiatric disorders
Common:
• Headache
• Depression
Uncommon:
• Confusion, sleepy or unable to sleep; nervousness; tingling or pins and needles like sensation in the hands or feet; vertigo (spinning sensation)
Rare:
• Abnormal dreams
• Sleep disorders
Eye disorders
Very common:
• Blurred vision

Cardiac and vascular disorders:
Very common:
• Dizziness

Common:
• Low blood pressure specially when standing up from sitting or lying down.
• Fainting
• Chest pain
• Irregular heart beat
• Heart related chest pain (angina pectoris)
• Increased heart rate

Uncommon:
• Sudden lowering of blood pressure when standing up from sitting or lying down.
• Palpitations
• Heart attack or stroke possibly due to excessive low blood pressure in high-risk patients (patients with blood flow disturbances to the heart or brain)

Rare:
• Raynaud's phenomenon (small arteries, usually in fingers and toes, go into spasm causing the skin to become pale or patchy red to blue colour)

Respiratory disorders:
Very common:
• Cough

Common:
• Shortness of breath

Uncommon:
• Runny nose
• Sore throat and hoarseness
• Asthma

Rare:
• Runny nose
• Pulmonary infiltrate (characterised by difficulty in breathing, coughing up blood, excessive sweating, anxiety, and pale skin)
• Swelling of the lining of nose
• Fluid in the lung

Gastrointestinal disorders:
Very common:
• Nausea

Common:
• diarrhoea
• abdominal pain
• alteration in taste

Uncommon:
• Severe abdominal pain (caused by inflammation of the pancreas)
• Vomiting
• Indigestion
• Constipation
• Loss of appetite
• Bubblly feeling in the stomach
• Dry mouth
• Peptic ulcer, (symptoms may be burning, aching pain with an empty feeling and hunger, particularly when the stomach is empty)

Very rare:
• Swelling of intestines causing abdominal pain

Hepatobiliary disorders:
Rare:
• Liver failure, inflammation of the liver, reduction or stoppage of bile flow from the bile duct in the liver (symptoms may be yellowing of the skin and whites of the eyes)

Skin and subcutaneous tissue disorders:
Common:
• Rash
• Itch, shortness of breath or wheezing and swelling of the hands, mouth, throat, face or eyes. Immediately seek medical attention if you experience these symptoms

Uncommon:
• Perspiration
• Itching
• Nettle-rash or hives
• Hair loss

Rare:
• Severe skin reaction (symptoms of which may be excessive redness of the skin, blisters, skin peeling off in sheets)

A complex side effect has also been reported which may include some or all of the following: fever, inflammation of the blood vessels, pain and inflammation of muscles and joints, blood disorders affecting the components of the blood and usually detected by a blood test, rash, hypersensitivity to sunlight and other effects on the skin.

Renal and urinary disorders:
Uncommon:
• Reduced kidney function or kidney failure (symptoms may be lower back pain and reduction in the volume of urine passed
• Presence of protein in the urine, which is usually detected by a test

Rare:
• Reduction in the amount of urine produced per day

Reproductive system and breast disorders:
Uncommon:
• Impotence

Rare:
• Enlargement of breasts in male

General disorders:
Very common:
• General weakness and tiredness

Common
• Fatigue

Uncommon:
• Muscle cramps
• Flushing
• Ringing of ears
• Fever
• Feeling unwell
Laboratory Tests:
Some side effects have been reported which affect the blood and are only detected by laboratory tests. These are:

Common:
- High levels of potassium
- Increases of creatinine

Uncommon:
- Increase of urea (waste products)
- Decreased levels of sodium

Rare:
- Elevated liver enzymes
- Raised levels of bilirubin (responsible for the yellow colour of bruises and the yellow discolouration in jaundice).

If you notice any of the above effects or if you have any other unusual symptoms or feelings, you should contact your doctor as soon as possible.

5. HOW TO STORE ENALAPRIL TABLETS
- Do not store above 25°C. Store in the original package. Do not put them into another container as they might get mixed up. Keep them in the pack in which they are supplied.
- Keep out of the reach and sight of children.
- Do not use Enalapril Tablets after the expiry date which is stated on the blister and the carton after EXP or EXP. DATE:
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Enalapril Tablets contains
The active substance is Enalapril Maleate. The other ingredients are Lactose, Maize Starch and Glycerol Distearate

What Enalapril Tablets look like and contents of the pack
Each tablet is white circular bliplanar uncoated with either 5, 10 or 20 embossed on one face and a score line on the other.
Enalapril 5 mg, 10 mg and 20 mg tablets are available in the packs of 28.
Enalapril 5 mg Tablets - PL 21880/0003
Enalapril 10 mg Tablets - PL 21880/0004
Enalapril 20 mg Tablets - PL 21880/0005

Further information is available on request.

Not all presentations are available in every country.

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