ENALAPRIL MALEATE 2.5MG, 5MG, 10MG AND 20MG TABLETS

PL 04543/0503-0505 and 0514

UKPAR

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The Medicines and Healthcare products Regulatory Agency granted CP Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg tablets (PL 04543/0503-0505 and 0514) on 9 June 2006. These products have been granted prescription only status.

Angiotensin converting enzyme (ACE) inhibitors similar to Enalapril Maleate have been available in the European Union, including the UK, for more than ten years. Their use is well established with recognised efficacy and acceptable safety.

Enalapril Maleate raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
ENALAPRIL MALEATE 2.5MG, 5MG, 10MG AND 20MG TABLETS

PL 04543/0503-0505 and 0514

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg tablets (PL 04543/0503-0505 and 0514) to CP Pharmaceuticals Limited. These ACE inhibitor tablets are prescription only products.

These national applications for Enalapril Maleate are submitted under EC, Article 10.1 of Directive 2001/83/EC.

Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg tablets contain the active ingredient enalapril maleate and are indicated for hypertension, congestive heart failure, prevention of symptomatic heart failure and prevention of coronary ischaemic events in patients with left ventricular dysfunction.
PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

This is a simple, piggy back application for Enalapril 2.5mg, 5mg, 10mg and 20mg Tablets submitted under Article 10.1 of Directive 2001/83/EC. The MA holder is CP Pharmaceuticals Limited.

These applications cross refer to piggy back applications for Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg tablets (PL 16002/012-0015), which are currently registered in the UK. The Marketing Authorisations for the latter are held by Pharmafile Ltd and a letter of informed consent is enclosed.

No issues or alerts are flagged for the reference product. In addition, no variations have been submitted or approved for the cross-reference products since submission of these applications.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s) and ATC Code

The proposed names of the products are Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg Tablets.
The proposed ATC code is correct.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain 2.5mg, 5mg, 10mg or 20mg of enalapril maleate and are packaged in Al/Al blisters or polypropylene containers with a silica gel desiccant and a white LDPE cap. The proposed pack-sizes are 28 tablets (blister) and 50 tablets (polypropylene container). These details are consistent with the details registered for the reference products.

For the 2.5mg and 5mg tablet the proposed shelf life (30 months) and storage conditions (“Do not store above 25°C”) are identical to the details registered for the reference product. For the 10mg and 20mg tablet the proposed shelf life (24 months) and storage conditions (“Do not store above 25°C”) are identical to the details registered for the reference product.

2.3 Legal status

On approval, the products will be subject to a medical prescription.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is CP Pharmaceuticals Limited, Ash Road North, Wrexham, Clyed, Wales, LL13 9UF and proof of establishment in the EU has been provided.
The QP responsible for pharmacovigilance is stated and her CV is included. The QP has broad ranging industrial experience and is appropriately qualified for her pharmacovigilance responsibilities.

2.5 Manufacturers

Product

Delta Limited, Reykjavikurvegi 78, PO Box 420, IS-222 Hafnarfjordur, Iceland is to be responsible for batch release and quality control of the finished product. This is consistent with the details registered for the reference products.

CP Pharmaceuticals is also listed as an importer and distributor and a valid Wholesale Dealer’s Licence is enclosed.

Actives:

The proposed active substance manufacturer listed is consistent with the details registered for the reference product. The applicant cross-refers to a drug master file, which has previously been assessed by the agency. Signed letters of access have been provided and the active substance manufacturer has committed to inform the applicant of any significant changes to the synthesis, purification, specifications or methods of analysis used in the manufacture and control of enalapril maleate.

2.6 Qualitative and quantitative composition

The proposed compositions are generally consistent with the details registered for the reference products. The proposed reference to standard for the active substance (Ph.Eur.) differs from the reference to standard registered for the reference products (USP). However, as Ph.Eur. specifications are tighter this is acceptable.

2.7 Manufacturing process

The proposed manufacturing process is generally consistent with the details registered for the reference product. Maximum batch sizes are also consistent.

2.8 Finished product/shelf-life specification

The proposed finished product specifications are generally consistent with the details registered for the reference products.

2.9 Drug substance specification

The drug substance specification is stated to comply with the Ph.Eur. (see 2.6) and includes additional controls for residual solvents. Controls for sulphated ash and heavy metals are stated as “USP” but acceptance limits comply with the Ph.Eur.

2.10 TSE Compliance
Lactose is the only material of animal origin in the products. Appropriate declarations have been provided by the finished product manufacturer and lactose supplier which indicate compliance with current guidance.

3. EXPERT REPORTS

A quality overall summary, non-clinical overview and clinical overview are enclosed. The reports indicate that the proposed products are identical to the reference products in terms of quality, safety and efficacy. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4.

4. PRODUCT NAME & APPEARANCE

The proposed product names are acceptable. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

All SPCs are satisfactory.

6. PATIENT INFORMATION LEAFLET/CARTON

These are satisfactory.

7. CONCLUSIONS

The data submitted with the applications are acceptable. A Marketing Authorisation should be granted to the applicant.
PRECLINICAL ASSESSMENT

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

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

QUALITY
The data for this application is consistent with that previously assessed for the cross-reference product 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
No new or unexpected safety concerns arise from this application.

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

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. The risk benefit ratio is considered to be positive.
ENALAPRIL MALEATE 2.5MG, 5MG, 10MG AND 20MG TABLETS

PL 04543/0503-0505 and 0514

**STEPS TAKEN FOR ASSESSMENT**

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<td>1</td>
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<td>Following assessment of the response, the MHRA requested further information relating to the quality dossier on 5 June 2006</td>
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<td>The applicant responded, providing further information on 6 June 2006</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

Enalapril Maleate 2.5mg Tablets (PL) has the following product summary:

1. **NAME OF THE MEDICINAL PRODUCT**

   Enalapril Maleate 2.5 mg Tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Enalapril Maleate 2.5mg

   For excipients, see 6.1

3. **PHARMACEUTICAL FORM**

   Tablets

   Circular white tablet marked E2.5. Diameter = 6mm.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic Indications**

   Hypertension: Treatment of all grades of essential hypertension, also renovascular hypertension.

   Congestive heart failure: Enalapril Maleate tablets should be used as an adjunctive therapy with digitalis and/ or non potassium-sparing diuretics as appropriate. Enalapril Maleate has been shown to improve symptoms, retard the progression of the disease, and reduce mortality and hospitalisation.

   Prevention of symptomatic heart failure: When used in asymptomatic patients with left ventricular dysfunction, Enalapril Maleate retards the development of symptomatic heart failure, and reduces hospitalisation for heart failure.

   Prevention of coronary ischaemic events in patients with left ventricular dysfunction: Enalapril Maleate reduces the incidence of myocardial infarction and reduces hospitalisation for unstable angina pectoris.

4.2. **Posology and Method of Administration**

   For oral use.

   The maximum daily dose is 40mg. Absorption is not affected by food.
Essential and renovascular hypertension:
A starting dose of 5mg once a day is recommended. Where concomitant therapy is a diuretic, the recommended initial dose of Enalapril Maleate is 2.5mg (see 'with concomitant diuretic therapy' section). The dose should be titrated to give optimum control of blood pressure. The usual maintenance dose is 10-20mg given once daily. In severe hypertension the dosage may be increased incrementally to a maximum of 40mg once daily.

The dosage of other antihypertensive agents being used together with Enalapril Maleate may need to be adjusted. Where Enalapril Maleate replaces a beta-blocking drug in the therapeutic regime, the beta-blocking agent should not be discontinued abruptly; the dosage should be titrated down after commencing therapy with Enalapril Maleate (see Manufacturer's recommendations).

With concomitant diuretic therapy: The recommended initial dose of Enalapril Maleate is 2.5mg. Symptomatic hypotension can occur following the initial dose of Enalapril Maleate; this is more likely when Enalapril Maleate is added to previous diuretic therapy. Caution is recommended, therefore, since these patients may be volume or salt-depleted. If possible, the diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalapril Maleate. Enalapril Maleate minimises the development of thiazide-induced hypokalaemia and hyperuricaemia.

Use in the elderly (over 65 years):
A reduced starting dose of 2.5mg is recommended in the elderly. Enalapril Maleate has been shown to be effective in the treatment of hypertension in the elderly, and some elderly patients may be more responsive to Enalapril Maleate than younger patients.

The dose should be titrated according to need for the control of blood pressure.

Heart failure/asymptomatic left ventricular dysfunction:
The recommended starting dose in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5mg once daily initiated under close medical supervision. For patients with severe heart failure, therapy should be initiated in hospital. Evidence of systolic left ventricular dysfunction should be obtained by relevant techniques (e.g. radionuclide ventriculography or echocardiography or equivalent) prior to initiation of preventative treatment; however, a repeated measurement may not be necessary in patients with one or more myocardial infarctions and documented reduction in cardiac function.

In patients with symptomatic heart failure, this dosage schedule has been shown to improve survival.

The dose should be titrated gradually over a two to four week period, or more rapidly if indicated by the residual signs and symptoms of heart failure, to the usual maintenance dose of 20mg given as a single dose or two divided doses, according to the tolerability of the patient.
Blood pressure and renal function should be monitored closely both before and during treatment with Enalapril Maleate. Serum potassium should also be monitored.

In order to decrease the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before introducing Enalapril Maleate. The appearance of hypotension after the initial dose of Enalapril Maleate does not preclude subsequent careful dose titration with the drug, following effective treatment of the hypotension.

Some patients are considered to be at higher risk when started on an ACE inhibitor and are recommended for initiation of therapy in hospital. Research data have shown such patients to be: those with severe heart failure; those on multiple or high-dose diuretics (e.g. > 80mg frusemide); patients with hypovolaemia; hyponatraemia (serum sodium < 130mmol/l); pre-existing hypotension (systolic blood pressure < 90mm Hg); patients with unstable cardiac failure; renal impairment (serum creatinine > 150 micromol/litre); those on high-dose vasodilator therapy; patients aged 70 years or over (see 'Precautions').

Use in impaired renal function:
Excretion is primarily by the renal route. Enalapril Maleate should therefore be used with caution in patients with renal impairment. The recommended starting dose is 2.5mg. The dose should be titrated against the response, and should be kept as low as possible to maintain adequate control of blood pressure or heart failure.

Enalapril Maleate is dialysable. Dialysis patients may be given the usual dose of Enalapril Maleate on dialysis days. A high incidence of anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with an ACE inhibitor. This combination should therefore be avoided. On the days when patients are not on dialysis the dosage should be tailored to the blood pressure response.

Children:
Not recommended. The paediatric use of Enalapril Maleate has not been studied.

4.3. Contra-indications
Enalapril Maleate is contra-indicated in pregnancy. When pregnancy is detected, treatment with Enalapril Maleate should be discontinued as soon as possible.

Hypersensitivity to the product or any of its components, and in patients with a history of angioneurotic oedema relating to previous treatment with an ACE inhibitor.
4.4. **Special Warnings and Special 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 has been seen only rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril Maleate, 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 Dosage and administration for management of these patients.)

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 contra-indication 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. 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 may become necessary.

The appearance of hypotension after the initial dose of Enalapril Maleate does not preclude subsequent careful dose titration with the drug after effective management of the hypotension.

**Impaired renal function:** Enalapril Maleate should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses. Close monitoring of renal function before and during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

Renal failure has been reported in association with Enalapril Maleate and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with Enalapril Maleate is usually reversible.
Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when Enalapril Maleate has been given concurrently with a diuretic. Dosage reduction of Enalapril Maleate and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see 'Renovascular hypertension').

Renovascular hypertension: Enalapril Maleate can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients treated with diuretics and/or those with renal insufficiency.

Angioneurotic oedema has been reported with angiotensin-converting enzyme inhibitors, including Enalapril Maleate. This may occur at any time during treatment. In such cases, Enalapril Maleate should be discontinued immediately and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients Should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5 ml 1:1000) should be administered promptly.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also 'Contra-indications').

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.

Haemodialysis patients: A high incidence of anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with and ACE inhibitor. This combination should therefore be avoided.

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.
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 diagnoses of cough.

Surgery/anaesthesia: In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Enalapril Maleate blocks angiotensin-II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

General: Where Enalapril Maleate has been used as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

Enalapril Maleate should not be used in patients with aortic stenosis or outflow obstruction.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other Medicinal products and other forms of Interaction

Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the antihypertensive efficacy of Enalapril Maleate. Adrenergic-blocking drugs should only be combined with Enalapril Maleate under careful supervision. Concomitant propranolol may reduce the bioavailability of Enalapril Maleate, but this does not appear to be of any clinical significance.

Concomitant therapy with lithium may increase the serum lithium concentration.

Plasma potassium usually remains within normal limits, although cases of hyperkalaemia have been reported. If Enalapril Maleate is given with a potassium-losing diuretic, the likelihood of diuretic-induced hypokalaemia may be lessened. Enalapril Maleate may elevate plasma potassium levels in patients with renal failure. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes are not recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. However, if the concomitant use of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

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 clinical trials with Enalapril Maleate have not confirmed these findings and do not preclude the use in diabetic patients. It is advised, however, that these patients be monitored.

_Narcotic drugs/antipsychotics:_ postural hypotension may occur with ACE inhibitors.

_Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids and procainamide:_ concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

_Non-steroid anti-inflammatory drugs:_ the administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of an ACE inhibitor. However, in a clinical pharmacology study, indometacin or sulindac was administered to hypertensive patients receiving Enalapril Maleate and there was no evidence of a blunting of the antihypertensive action of Enalapril Maleate. Furthermore, it has been described that NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. these effects are in principle reversible, and occur especially in patients with compromised renal function.

_Antacids:_ induce decreased bioavailability of ACE inhibitors.

_Sympathomimetics:_ may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored, to confirm that the desired effect is being obtained.

_Alcohol:_ enhances the hypotensive effect with ACE inhibitors.

_Ciclosporin:_ increases the risk of hyperkalaemia with ACE inhibitors.

4.6. **Pregnancy and Lactation**

Enalapril Maleate has been shown to be foetotoxic in rabbits during middle and late pregnancy.

Foetal exposure in humans during the second and third trimesters of pregnancy has been associated with foetal and neonatal morbidity and mortality.

ACE inhibitors in human pregnancy have been associated with oligohydramnios which may result in limb contractures, craniofacial deformations and hypoplastic lung development. Hypotension, renal failure, hyperkalaemia and skull hypoplasia have occurred in the new-born. These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE-inhibitor exposure limited to the first trimester.

Because of these findings, Enalapril Maleate is contraindicated in pregnancy. When pregnancy is detected, treatment with Enalapril Maleate should be discontinued as soon as possible.
Breast feeding mothers: Enalapril Maleate and Enalaprilat are excreted in human milk; caution should be exercised if Enalapril Maleate is given to breast-feeding mothers.

4.7. Effects on Ability to Drive and Use Machines

There is no data to suggest that Enalapril Maleate affects the ability to drive and use machines.

4.8. Undesirable Effects

Severe hypotension and renal failure have occurred in association with therapy with Enalapril Maleate. These appear to occur in certain specific sub-groups.

Other adverse reactions: Dizziness and headaches are the most commonly reported side effects. Less frequently, fatigue, asthenia, hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, rash, and cough have been reported. Even less frequently, renal dysfunction, renal failure, and oliguria have been reported.

Rarely reported side-effects include:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to severe hypotension in high-risk patients (see 'Precautions'), chest pain, palpitations, rhythm disturbances, angina pectoris.

Gastro-intestinal: Ileus, pancreatitis, hepatic failure, hepatitis-either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

Nervous system/Psychiatric: Depression, confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo.

Respiratory: Pulmonary infiltrates, bronchospasm, asthma, dyspnoea, rhinorrhoea, sore throat and hoarseness.

Skin: Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, alopecia.

Other: Impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision. A complex of symptoms has been reported which may include fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.
Hypersensitivity/Angioneurotic oedema: Angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see 'Precautions').

Laboratory test findings: Increases in blood urea and plasma creatinine, reversible on discontinuation of Enalapril Maleate, are most likely in the presence of severe heart failure or bilateral renal artery stenosis, especially in patients with renal insufficiency (see 'Precautions'). However, increases in blood urea and plasma creatinine may occur without evidence of pre-existing renal impairment, especially in patients taking diuretics. In this event undiagnosed renal artery stenosis should be suspected. Dosage reduction of Enalapril Maleate and/or discontinuation of the diuretic should be considered.

Hyperkalaemia and Hyponatraemia have also been reported in a few cases.

Decreases in haemoglobin and haematocrit as well as elevation of liver enzymes and/or serum bilirubin have been reported in a few patients, and are usually reversible upon discontinuation of Enalapril Maleate.

Decreases in platelets and white cell count, and rare cases of neutropenia, thrombocytopenia, bone marrow depression, and agranulocytosis have been reported, but a causal relationship to Enalapril Maleate has not been established.

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 system, and stupor. Serum Enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300mg and 440mg of Enalapril Maleate, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If ingestion is recent, induce emesis. Enalapril Maleate can be removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ATC code: C09A A02 Group: ACE inhibitors, plain

Following oral administration, Enalapril Maleate is rapidly absorbed and hydrolysed to Enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor. Enalaprilat modulates a specific physiological mechanism, the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure. Onset of action begins smoothly and gradually within one hour and the effects continue usually for 24 hours after a single daily dose.
Data indicate no loss of effect during long term therapy. Rebound hypertension does not occur following abrupt cessation of therapy.

Congestive heart failure patients benefit particularly from reduction in pre-load and after-load of the heart, with an increase in cardiac output, without reflex tachycardia.

5.2. Pharmacokinetic Properties

Following oral administration, peak serum concentrations occur within one hour. Based on urinary recovery, the extent of absorption is approximately 60%. The absorption of Enalapril Maleate is not affected by food. Peak serum concentrations occur three to four hours after an oral dose. Excretion is primary renal. Approximately 94% of the dose is recovered in the urine and faeces as Enalapril Maleate or Enalaprilat. Enalaprilat is 50% to 60% bound to plasma proteins, its elimination is multiphasic with a half life of 11 hours after multiple doses to patients with normal renal function.

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 Maleate does not have serious adverse effects on fertility and reproductive performance in rats, and it is not teratogenic. It crosses the placenta and has been shown to be foetotoxic in rabbits during middle and late pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

croscarmellose sodium
lactose monohydrate
magnesium stearate
pregelatinised maize starch
sodium hydrogen carbonate

6.2. Incompatibilities

Not Applicable

6.3. Shelf Life

30 months.
6.4. **Special Precautions for Storage**

Do not store above 25°C.

6.5. **Nature and Contents of Container**

Al/Al blisters: Pack sizes 28 tablets
Securitainer: Pack sizes 50 tablets

6.6. **Instruction for Use/Handling**

No special instructions.

7. **MARKETING AUTHORIZATION HOLDER**

CP Pharmaceuticals Limited
Ash Road North,
Wrexham
Clywd
Wales
LL13 9UF

8. **MARKETING AUTHORIZATION NUMBER**

PL 04543/0504

9. **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

09/06/2006

10. **DATE OF REVISION OF THE TEXT**

09/06/2006

Enalapril Maleate 5mg Tablets (PL) has the following product summary:

1. **NAME OF THE MEDICINAL PRODUCT**
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Enalapril Maleate 5 mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablets
Circular white tablet with a score on one side and marked E5 on the other side. Diameter 8mm

CLINICAL PARTICULARS

4.1. Therapeutic Indications

Hypertension: Treatment of all grades of essential hypertension, also renovascular hypertension.

Congestive heart failure: Enalapril Maleate tablets should be used as an adjunctive therapy with digitalis and/or non potassium-sparing diuretics as appropriate. Enalapril Maleate has been shown to improve symptoms, retard the progression of the disease, and reduce mortality and hospitalisation.

Prevention of symptomatic heart failure: When used in asymptomatic patients with left ventricular dysfunction, Enalapril Maleate retards the development of symptomatic heart failure, and reduces hospitalisation for heart failure.

Prevention of coronary ischaemic events in patients with left ventricular dysfunction: Enalapril Maleate reduces the incidence of myocardial infarction and reduces hospitalisation for unstable angina pectoris.

4.2. Posology and Method of Administration

For oral use.

The maximum daily dose is 40 mg. Absorption is not affected by food.

Essential and renovascular hypertension:
A starting dose of 5 mg once a day is recommended. Where concomitant therapy is a diuretic, the recommended initial dose of Enalapril Maleate is 2.5 mg (see 'with concomitant diuretic therapy' section). The dose should be titrated to give optimum control of blood pressure. The usual maintenance
dose is 10-20 mg given once daily. In severe hypertension the dosage may be increased incrementally to a maximum of 40 mg once daily.

The dosage of other antihypertensive agents being used together with Enalapril Maleate may need to be adjusted. Where Enalapril Maleate replaces a beta-blocking drug in the therapeutic regime, the beta-blocking agent should not be discontinued abruptly; the dosage should be titrated down after commencing therapy with Enalapril Maleate (see Manufacturer's recommendations).

With concomitant diuretic therapy: The recommended initial dose of Enalapril Maleate is 2.5 mg. Symptomatic hypotension can occur following the initial dose of Enalapril Maleate; this is more likely when Enalapril Maleate is added to previous diuretic therapy. Caution is recommended, therefore, since these patients may be volume or salt-depleted. If possible, the diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalapril Maleate. Enalapril Maleate minimises the development of thiazide-induced hypokalaemia and hyperuricaemia.

Use in the elderly (over 65 years):
A reduced starting dose of 2.5 mg is recommended in the elderly. Enalapril Maleate has been shown to be effective in the treatment of hypertension in the elderly, and some elderly patients may be more responsive to Enalapril Maleate than younger patients.

The dose should be titrated according to need for the control of blood pressure.

Heart failure/asymptomatic left ventricular dysfunction:
The recommended starting dose in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg once daily initiated under close medical supervision. For patients with severe heart failure, therapy should be initiated in hospital. Evidence of systolic left ventricular dysfunction should be obtained by relevant techniques (e.g. radionuclide ventriculography or echocardiography or equivalent), prior to initiation of preventative treatment; however, a repeated measurement may not be necessary in patients with one or more myocardial infarctions and documented reduction in cardiac function.

In patients with symptomatic heart failure, this dosage schedule has been shown to improve survival.

The dose should be titrated gradually over a two to four week period, or more rapidly if indicated by the residual signs and symptoms of heart failure, to the usual maintenance dose of 20 mg given as a single dose or two divided doses, according to the tolerability of the patient.

Blood pressure and renal function should be monitored closely both before and during treatment with Enalapril Maleate. Serum potassium should also be monitored.
In order to decrease the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before introducing Enalapril Maleate. The appearance of hypotension after the initial dose of Enalapril Maleate does not preclude subsequent careful dose titration with the drug, following effective treatment of the hypotension.

Some patients are considered to be at higher risk when started on an ACE inhibitor and are recommended for initiation of therapy in hospital. Research data have shown such patients to be: those with severe heart failure; those on multiple or high-dose diuretics (e.g. > 80 mg frusemide); patients with hypovolaemia; hyponatraemia (serum sodium < 130 mmol/L); pre-existing hypotension (systolic blood pressure < 90 mm Hg); patients with unstable cardiac failure; renal impairment (serum creatinine > 150 micromol/litre); those on high-dose vasodilator therapy; patients aged 70 years or over (see 'Precautions').

Use in impaired renal function:
Excretion is primarily by the renal route. Enalapril Maleate should therefore be used with caution in patients with renal impairment. The recommended starting dose is 2.5 mg. The dose should be titrated against the response, and should be kept as low as possible to maintain adequate control of blood pressure or heart failure.

Enalapril Maleate is dialysable. Dialysis patients may be given the usual dose of Enalapril Maleate on dialysis days. A high incidence of anaphylactoid reactions have been reported in patient dialysed with high-flux membranes and treated concomitantly with an ACE inhibitor. This combination should therefore be avoided. On the days when patients are not on dialysis the dosage should be tailored to the blood pressure response.

Children:
Not recommended. The paediatric use of Enalapril Maleate has not been studied.

4.3. Contra-indications
Enalapril Maleate is contra-indicated in pregnancy. When pregnancy is detected, treatment with Enalapril Maleate should be discontinued as soon as possible.

Hypersensitivity to the product or any of its components, and in patients with a history of angioneurotic oedema relating to previous treatment with an ACE inhibitor.

4.4. Special Warnings and Special 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 has been seen only rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril Maleate, 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 Dosage and administration for management of these patients.)

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 contra-indication 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. 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 may become necessary.

The appearance of hypotension after the initial dose of Enalapril Maleate does not preclude subsequent careful dose titration with the drug after effective management of the hypotension.

Impaired renal function: Enalapril Maleate should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses. Close monitoring of renal function before and during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

Renal failure has been reported in association with Enalapril Maleate and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with Enalapril Maleate is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when Enalapril Maleate has
been given concurrently with a diuretic. Dosage reduction of Enalapril Maleate and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see 'Renovascular hypertension').

Renovascular hypertension: Enalapril Maleate can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients treated with diuretics and/or those with renal insufficiency.

Angioneurotic oedema has been reported with angiotensin-converting enzyme inhibitors, including Enalapril Maleate. This may occur at any time during treatment. In such cases, Enalapril Maleate should be discontinued immediately and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients Should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5 mL 1:1000) should be administered promptly.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also 'Contra-indications').

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.

Haemodialysis patients: A high incidence of anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with and ACE inhibitor. This combination should therefore be avoided.

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.

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 diagnoses of cough.
Surgery/anaesthesia: In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Enalapril Maleate blocks angiotensin-II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

General: Where Enalapril Maleate has been used as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

Enalapril Maleate should not be used in patients with aortic stenosis or outflow obstruction.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other Medicinal Products and other forms of Interaction

Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the antihypertensive efficacy of Enalapril Maleate. Adrenergic-blocking drugs should only be combined with Enalapril Maleate under careful supervision. Concomitant propranolol may reduce the bioavailability of Enalapril Maleate, but this does not appear to be of any clinical significance.

Concomitant therapy with lithium may increase the serum lithium concentration.

Plasma potassium usually remains within normal limits, although cases of hyperkalaemia have been reported. If Enalapril Maleate is given with a potassium-losing diuretic, the likelihood of diuretic-induced hypokalaemia may be lessened. Enalapril Maleate may elevate plasma potassium levels in patients with renal failure. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes are not recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. However, if the concomitant use of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulin, 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 clinical trials with Enalapril Maleate have not confirmed these findings and do not preclude the use in diabetic patients. It is advised, however, that these patients be monitored.
Narcotic drugs/antipsychotics: postural hypotension may occur with ACE inhibitors.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids and procaainamide: concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

Non-steroid anti-inflammatory drugs: the administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of an ACE inhibitor. However, in a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving Enalapril Maleate and there was no evidence of a blunting of the antihypertensive action of Enalapril Maleate. Furthermore, it has been described that NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function.

Antacids: induce decreased bioavailability of ACE inhibitors.

Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored, to confirm that the desired effect is being obtained.

Alcohol: enhances the hypotensive effect with ACE inhibitors.

Ciclosporin: increases the risk of hyperkalaemia with ACE inhibitors.

4.6. Pregnancy and Lactation

Enalapril has been shown to be foetotoxic in rabbits during middle and late pregnancy.

Foetal exposure in humans during the second and third trimesters of pregnancy has been associated with foetal and neonatal morbidity and mortality.

ACE inhibitors in human pregnancy have been associated with oligohydramnios which may result in limb contractures, craniofacial deformations and hypoplastic lung development. Hypotension, renal failure, hyperkalaemia and skull hypoplasia have occurred in the new-born. These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE-inhibitor exposure limited to the first trimester.

Because of these findings, Enalapril Maleate is contraindicated in pregnancy. When pregnancy is detected, treatment with Enalapril Maleate should be discontinued as soon as possible.

Breast feeding mothers: Enalapril Maleate and Enalaprilat are excreted in human milk; caution should be exercised if Enalapril Maleate is given to breast-feeding mothers.
4.7. **Effects on Ability to Drive and Use Machines**

There is no data to suggest that Enalapril Maleate affects the ability to drive and use machines.

4.8. **Undesirable Effects**

Severe hypotension and renal failure have occurred in association with therapy with Enalapril Maleate. These appear to occur in certain specific sub-groups.

Other adverse reactions: Dizziness and headaches are the most commonly reported side effects. Less frequently, fatigue, asthenia, hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, rash, and cough have been reported. Even less frequently, renal dysfunction, renal failure, and oliguria have been reported.

Rarely reported side-effects include:

**Cardiovascular:** Myocardial infarction or cerebrovascular accident, possibly secondary to severe hypotension in high-risk patients (see 'Precautions'), chest pain, palpitations, rhythm disturbances, angina pectoris.

**Gastro-intestinal:** Ileus, pancreatitis, hepatic failure, hepatitis-either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

**Nervous system/Psychiatric:** Depression, confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo.

**Respiratory:** Pulmonary infiltrates, bronchospasm, asthma, dyspnoea, rhinorrhoea, sore throat and hoarseness.

**Skin:** Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, alopecia.

**Other:** Impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision. A complex of symptoms has been reported which may include fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

**Hypersensitivity/Angioneurotic oedema:** Angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see 'Precautions').

MHRA PAR Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg Tablets, PL 04543/0503-05 & 0514
Laboratory test findings: Increases in blood urea and plasma creatinine, reversible on discontinuation of Enalapril Maleate, are most likely in the presence of severe heart failure or bilateral renal artery stenosis, especially in patients with renal insufficiency (see 'Precautions'). However, increases in blood urea and plasma creatinine may occur without evidence of pre-existing renal impairment, especially in patients taking diuretics. In this event undiagnosed renal artery stenosis should be suspected. Dosage reduction of Enalapril Maleate and/or discontinuation of the diuretic should be considered.

Hyperkalaemia and hyponatraemia have also been reported in a few cases.

Decreases in haemoglobin and haematocrit as well as elevation of liver enzymes and/or serum bilirubin have been reported in a few patients, and are usually reversible upon discontinuation of Enalapril Maleate.

Decreases in platelets and white cell count, and rare cases of neutropenia, thrombocytopenia, bone marrow depression, and agranulocytosis have been reported, but a causal relationship to Enalapril Maleate has not been established.

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 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 Maleate, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If ingestion is recent, induce emesis. Enalapril Maleate can be removed from the general circulation by haemodialysis.

PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Following oral administration, Enalapril Maleate is rapidly absorbed and hydrolysed to Enalaprilat, a highly specific, long-acting, non-sulphhydryl angiotensin-converting enzyme inhibitor. Enalaprilat modulates a specific physiological mechanism, the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure. Onset of action begins smoothly and gradually within one hour and the effects continue usually for 24 hours after a single daily dose.

Data indicate no loss of effect during long term therapy. Rebound hypertension does not occur following abrupt cessation of therapy.
Congestive heart failure patients benefit particularly from reduction in pre-load and after-load of the heart, with an increase in cardiac output, without reflex tachycardia.

5.2. Pharmacokinetic Properties

Following oral administration, peak serum concentrations occur within one hour. Based on urinary recovery, the extent of absorption is approximately 60%. The absorption of Enalapril Maleate is not affected by food. Peak serum concentrations occur three to four hours after an oral dose. Excretion is primary renal. Approximately 94% of the dose is recovered in the urine and faeces as Enalapril Maleate or Enalaprilat. Enalaprilat is 50% to 60% bound to plasma proteins, its elimination is multiphasic with a half life of 11 hours after multiple doses to patients with normal renal function.

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 Maleate does not have serious adverse effects on fertility and reproductive performance in rats, and it is not teratogenic. It crosses the placenta and has been shown to be foetotoxic in rabbits during middle and late pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipient(s)

croscarmellose sodium,
lactose monohydrate,
magnesium stearate,
pregelatinised maize starch,
sodium hydrogen carbonate
Red iron oxide (E172)
Yellow iron oxide (E172).

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

30 months
6.4. Special Precautions for Storage

Do not store above 25 °C

6.5. Nature and Contents of Container

Al/Al blisters: Pack sizes 28 tablets
Securitainer: Pack sizes 50 tablets

6.6. Instruction for Use/Handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Limited
Ash Road North,
Wrexham
Clywd
Wales
LL13 9UF

8. MARKETING AUTHORISATION NUMBER

PL 04543/0514

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/06/2006

10. DATE OF REVISION OF THE TEXT

09/06/2006

Enalapril Maleate 10mg Tablets (PL) has the following product summary:

1. NAME OF THE MEDICINAL PRODUCT

Enalapril Maleate 10mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Enalapril Maleate 10mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablets
Circular peach tablet with a score on one side and marked E10 on the other side. Diameter 7mm

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hypertension: Treatment of all grades of essential hypertension, also renovascular hypertension.

Congestive heart failure: Enalapril tablets should be used as an adjunctive therapy with digitalis and/or non potassium-sparing diuretics as appropriate. Enalapril has been shown to improve symptoms, retard the progression of the disease, and reduce mortality and hospitalisation.

Prevention of symptomatic heart failure: When used in asymptomatic patients with left ventricular dysfunction, enalapril retards the development of symptomatic heart failure, and reduces hospitalisation for heart failure.

Prevention of coronary ischaemic events in patients with left ventricular dysfunction: Enalapril reduces the incidence of myocardial infarction and reduces hospitalisation for unstable angina pectoris.

4.2. Posology and method of administration

For oral use.

The maximum daily dose is 40mg.

Essential and renovascular hypertension:
A starting dose of 5mg once a day is recommended. Where concomitant therapy is a diuretic, the recommended initial dose of enalapril is 2.5mg (see 'with concomitant diuretic therapy' section). The dose should be titrated to give optimum control of blood pressure. The usual maintenance dose is 10-20mg given once daily. In severe hypertension the dosage may be increased incrementally to a maximum of 40mg once daily.

The dosage of other antihypertensive agents being used together with enalapril may need to be adjusted. Where enalapril replaces a beta-blocking drug in the therapeutic regime, the beta-blocking agent should not be discontinued.
abruptly; the dosage should be titrated down after commencing therapy with enalapril (see Manufacturer's recommendations).

With concomitant diuretic therapy: The recommended initial dose of enalapril is 2.5mg. Symptomatic hypotension can occur following the initial dose of enalapril; this is more likely when enalapril is added to previous diuretic therapy. Caution is recommended, therefore, since these patients may be volume or salt-depleted. If possible, the diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with enalapril. Enalapril minimises the development of thiazide-induced hypokalaemia and hyperuricaemia.

Use in the elderly (over 65 years):
A reduced starting dose of 2.5mg is recommended in the elderly. Enalapril has been shown to be effective in the treatment of hypertension in the elderly, and some elderly patients may be more responsive to enalapril than younger patients.

The dose should be titrated according to need for the control of blood pressure.

Heart failure/asymptomatic left ventricular dysfunction:
The recommended starting dose in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5mg once daily initiated under close medical supervision. For patients with severe heart failure, therapy should be initiated in hospital. Evidence of systolic left ventricular dysfunction should be obtained by relevant techniques (e.g. radionuclide ventriculography or echocardiography or equivalent) prior to initiation of preventative treatment; however, a repeated measurement may not be necessary in patients with one or more myocardial infarctions and documented reduction in cardiac function.

In patients with symptomatic heart failure, this dosage schedule has been shown to improve survival.

The dose should be titrated gradually over a two to four week period, or more rapidly if indicated by the residual signs and symptoms of heart failure, to the usual maintenance dose of 20mg given as a single dose or two divided doses, according to the tolerability of the patient.

Blood pressure and renal function should be monitored closely both before and during treatment with enalapril. Serum potassium should also be monitored.

In order to decrease the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before introducing enalapril. The appearance of hypotension after the initial dose of enalapril does not preclude subsequent careful dose titration with the drug, following effective treatment of the hypotension.

Some patients are considered to be at higher risk when started on an ACE inhibitor and are recommended for initiation of therapy in hospital. Research
data have shown such patients to be: those with severe heart failure; those on
multiple or high-dose diuretics (e.g. > 80mg frusemide); patients with
hypovolaemia; hyponatraemia (serum sodium < 130 mmol/L); pre-existing
hypotension (systolic blood pressure < 90 mm Hg); patients with unstable
cardiac failure; renal impairment (serum creatinine > 150 µmol/L); those on
high-dose vasodilator therapy; patients aged 70 years or over (see 'Precautions').

Use in impaired renal function:
Excretion is primarily by the renal route. Enalapril should therefore be used
with caution in patients with renal impairment. The recommended starting
dose is 2.5mg. The dose should be titrated against the response, and should be
kept as low as possible to maintain adequate control of blood pressure or heart
failure.

Enalapril is dialysable. Dialysis patients may be given the usual dose of
enalapril on dialysis days. A high incidence of anaphylactoid reactions have
been reported in patient dialysed with high-flux membranes and treated
concomitantly with an ACE inhibitor. This combination should therefore be
avoided. On the days when patients are not on dialysis the dosage should be
tailored to the blood pressure response.

Children:
Not recommended. The paediatric use of enalapril has not been studied.

4.3. Contraindications
Enalapril is contra-indicated in pregnancy. When pregnancy is detected,
treatment with enalapril should be discontinued as soon as possible.

Hypersensitivity to the product or any of its components, and in patients with a
history of angioneurotic oedema relating to previous treatment with an ACE
inhibitor.

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 has been seen only rarely in uncomplicated
hypertensive patients. In hypertensive patients receiving enalapril,
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 Dosage and administration for management of these patients.)

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 contra-indication 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. 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 may become necessary.

The appearance of hypotension after the initial dose of enalapril does not preclude subsequent careful dose titration with the drug after effective management of the hypotension.

Impaired renal function: Enalapril should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses. Close monitoring of renal function before and during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with enalapril is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see 'Renovascular hypertension')

Renovascular hypertension: Enalapril can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients treated with diuretics and/or those with renal insufficiency.
Angioneurotic oedema has been reported with angiotensin-converting enzyme inhibitors, including enalapril. This may occur at any time during treatment. In such cases, enalapril should be discontinued immediately and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5mL 1:1000) should be administered promptly.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also 'Contra-indications'). 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.

Haemodialysis patients: A high incidence of anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with and ACE inhibitor. This combination should therefore be avoided.

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.

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 diagnoses of cough.

Surgery/anaesthesia: In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, enalapril blocks angiotensin-II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

General: Where enalapril has been used as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

Enalapril should not be used in patients with aortic stenosis or outflow obstruction.
4.5. Interactions with other medicinal products and other forms of interaction

Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the antihypertensive efficacy of enalapril. Adrenergic-blocking drugs should only be combined with enalapril under careful supervision. Concomitant propranolol may reduce the bioavailability of enalapril, but this does not appear to be of any clinical significance.

Concomitant therapy with lithium may increase the serum lithium concentration.

Plasma potassium usually remains within normal limits, although cases of hyperkalaemia have been reported. If enalapril is given with a potassium-losing diuretic, the likelihood of diuretic-induced hypokalaemia may be lessened. Enalapril may elevate plasma potassium levels in patients with renal failure. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes are not recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. However, if the concomitant use of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulin, 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 clinical trials with enalapril have not confirmed these findings and do not preclude the use in diabetic patients. It is advised, however, that these patients be monitored.

Narcotic drugs/antipsychotics: postural hypotension may occur with ACE inhibitors.

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

Non-steroid anti-inflammatory drugs: the administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of an ACE inhibitor. However, in a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving enalapril and there was no evidence of a blunting of the antihypertensive action of enalapril. Furthermore, it has been described that NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function.
Antacids: induce decreased bioavailability of ACE inhibitors.

Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored, to confirm that the desired effect is being obtained.

Alcohol: enhances the hypotensive effect with ACE inhibitors.

Ciclosporin: increases the risk of hyperkalaemia with ACE inhibitors.

4.6. Pregnancy and lactation

Enalapril has been shown to be foetotoxic in rabbits during middle and late pregnancy.

Foetal exposure in humans during the second and third trimesters of pregnancy has been associated with foetal and neonatal morbidity and mortality.

ACE inhibitors in human pregnancy have been associated with oligohydramnios which may result in limb contractures, craniofacial deformations and hypoplastic lung development. Hypotension, renal failure, hyperkalaemia and skull hypoplasia have occurred in the new-born. These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE-inhibitor exposure limited to the first trimester.

Because of these findings, enalapril is contraindicated in pregnancy. When pregnancy is detected, treatment with enalapril should be discontinued as soon as possible.

Breast feeding mothers: Enalapril and enalaprilat are excreted in human milk; caution should be exercised if enalapril is given to breast-feeding mothers.

4.7. Effects on ability to drive and use machines

There is no data to suggest that enalapril affects the ability to drive and use machines.

4.8. Undesirable effects

Severe hypotension and renal failure have occurred in association with therapy with enalapril. These appear to occur in certain specific sub-groups.

Other adverse reactions: Dizziness and headaches are the most commonly reported side effects. Less frequently, fatigue, asthenia, hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, rash, and
cough have been reported. Even less frequently, renal dysfunction, renal failure, and oliguria have been reported.

Rarely reported side-effects include:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to severe hypotension in high-risk patients (see 'Precautions'), chest pain, palpitations, rhythm disturbances, angina pectoris.

Gastro-intestinal: Ileus, pancreatitis, hepatic failure, hepatitis-either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

Nervous system/Psychiatric: Depression, confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo.

Respiratory: Pulmonary infiltrates, bronchospasm, asthma, dyspnoea, rhinorrhoea, sore throat and hoarseness.

Skin: Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, alopecia.

Other: Impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision.

A complex of symptoms has been reported which may include fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

Hypersensitivity/Angioneurotic oedema: Angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see 'Precautions').

Laboratory test findings: Increases in blood urea and plasma creatinine, reversible on discontinuation of enalapril, are most likely in the presence of severe heart failure or bilateral renal artery stenosis, especially in patients with renal insufficiency (see 'Precautions'). However, increases in blood urea and plasma creatinine may occur without evidence of pre-existing renal impairment, especially in patients taking diuretics. In this event undiagnosed renal artery stenosis should be suspected. Dosage reduction of enalapril and/or discontinuation of the diuretic should be considered.

Hyperkalaemia and hyponatraemia have also been reported in a few cases.

Decreases in haemoglobin and haematocrit as well as elevation of liver enzymes and/or serum bilirubin have been reported in a few patients, and are usually reversible upon discontinuation of enalapril.
Decreases in platelets and white cell count, and rare cases of neutropenia, thrombocytopenia, bone marrow depression, and agranulocytosis have been reported, but a causal relationship to enalapril has not been established.

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 system, and stupor. Serum enalaprilat levels 100 times and 200 times higher than usually seen after therapeutic doses have been reported after ingestion of 300mg and 440mg of enalapril, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If ingestion is recent, induce emesis. Enalapril can be removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Following oral administration, enalapril is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor. Enalaprilat modulates a specific physiological mechanism, the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure. Onset of action begins smoothly and gradually within one hour and the effects continue usually for 24 hours after a single daily dose.

Data indicate no loss of effect during long term therapy. Rebound hypertension does not occur following abrupt cessation of therapy.

Congestive heart failure patients benefit particularly from reduction in pre-load and after-load of the heart, with an increase in cardiac output, without reflex tachycardia.

5.2. Pharmacokinetic properties

Following oral administration, peak serum concentrations occur within one hour. Based on urinary recovery, the extent of absorption is approximately 60%. Peak serum concentrations occur three to four hours after an oral dose. Excretion is primary renal. Approximately 94% of the dose is recovered in the urine and faeces as enalaprilat or enalapril. Enalaprilat is 50% to 60% bound to plasma proteins, its elimination is multiphasic with a half life of 11 hours after multiple doses to patients with normal renal function.
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 does not have serious adverse effects on fertility and reproductive performance in rats, and it is not teratogenic. It crosses the placenta and has been shown to be foetotoxic in rabbits during middle and late pregnancy.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**

- Croscarmellose sodium
- Lactose monohydrate
- Magnesium stearate
- Pregelatinised maize starch
- Sodium hydrogen carbonate
- Red iron oxide (E172)
- Yellow iron oxide (E172).

6.2. **Incompatibilities**

Not applicable.

6.3. **Shelf life**

24 months.

6.4. **Special precautions for storage**

Do not store above 25 °C

6.5. **Nature and contents of container**

- Al/Al blisters: Pack sizes 28 tablets
- Securitainer: Pack sizes 50 tablets

6.6. **Instruction for Use/Handling**

No special instructions.

7. **MARKETING AUTHORISATION HOLDER**
8. MARKETING AUTHORISATION NUMBER

PL 04543/0503

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/06/2006

10. DATE OF REVISION OF THE TEXT

09/06/2006

Enalapril Maleate 20mg Tablets (PL) has the following product summary:

1. NAME OF THE MEDICINAL PRODUCT

Enalapril Maleate 20 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Enalapril Maleate 20 mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablets

Circular orange tablets with a score on one side and marked E20 on the other side. Diameter 9mm.

4. CLINICAL PARTICULARS
4.1. Therapeutic Indications

Hypertension: Treatment of all grades of essential hypertension, also renovascular hypertension.

Congestive heart failure: Enalapril Maleate tablets should be used as an adjunctive therapy with digitalis and/ or non potassium-sparing diuretics as appropriate. Enalapril Maleate has been shown to improve symptoms, retard the progression of the disease, and reduce mortality and hospitalisation.

Prevention of symptomatic heart failure: When used in asymptomatic patients with left ventricular dysfunction, Enalapril Maleate retards the development of symptomatic heart failure, and reduces hospitalisation for heart failure.

Prevention of coronary ischaemic events in patients with left ventricular dysfunction: Enalapril Maleate reduces the incidence of myocardial infarction and reduces hospitalisation for unstable angina pectoris.

4.2. Posology and Method of Administration

For oral use.

The maximum daily dose is 40 mg. Absorption is not affected by food.

Essential and renovascular hypertension:
A starting dose of 5 mg once a day is recommended. Where concomitant therapy is a diuretic, the recommended initial dose of Enalapril Maleate is 2.5 mg (see 'with concomitant diuretic therapy' section). The dose should be titrated to give optimum control of blood pressure. The usual maintenance dose is 10-20 mg given once daily. In severe hypertension the dosage may be increased incrementally to a maximum of 40 mg once daily.

The dosage of other antihypertensive agents being used together with Enalapril Maleate may need to be adjusted. Where Enalapril Maleate replaces a beta-blocking drug in the therapeutic regime, the beta-blocking agent should not be discontinued abruptly; the dosage should be titrated down after commencing therapy with Enalapril Maleate (see Manufacturer's recommendations).

With concomitant diuretic therapy: The recommended initial dose of Enalapril Maleate is 2.5 mg. Symptomatic hypotension can occur following the initial dose of Enalapril Maleate; this is more likely when Enalapril Maleate is added to previous diuretic therapy. Caution is recommended, therefore, since these patients may be volume or salt-depleted. If possible, the diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with Enalapril Maleate. Enalapril Maleate minimises the development of thiazide-induced hypokalaemia and hyperuricaemia.

Use in the elderly (over 65 years):
A reduced starting dose of 2.5 mg is recommended in the elderly. Enalapril Maleate has been shown to be effective in the treatment of hypertension in the elderly, and some elderly patients may be more responsive to Enalapril Maleate than younger patients.

The dose should be titrated according to need for the control of blood pressure.

Heart failure/asymptomatic left ventricular dysfunction:
The recommended starting dose in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg once daily initiated under close medical supervision. For patients with severe heart failure, therapy should be initiated in hospital. Evidence of systolic left ventricular dysfunction should be obtained by relevant techniques (e.g. radionuclide ventriculography or echocardiography or equivalent) prior to initiation of preventative treatment; however, a repeated measurement may not be necessary in patients with one or more myocardial infarctions and documented reduction in cardiac function.

In patients with symptomatic heart failure, this dosage schedule has been shown to improve survival.

The dose should be titrated gradually over a two to four week period, or more rapidly if indicated by the residual signs and symptoms of heart failure, to the usual maintenance dose of 20 mg given as a single dose or two divided doses, according to the tolerability of the patient.

Blood pressure and renal function should be monitored closely both before and during treatment with Enalapril Maleate. Serum potassium should also be monitored.

In order to decrease the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before introducing Enalapril Maleate. The appearance of hypotension after the initial dose of Enalapril Maleate does not preclude subsequent careful dose titration with the drug, following effective treatment of the hypotension.

Some patients are considered to be at higher risk when started on an ACE inhibitor and are recommended for initiation of therapy in hospital. Research data have shown such patients to be: those with severe heart failure; those on multiple or high-dose diuretics (e.g. > 80 mg frusemide); patients with hypovolaemia; hyponatraemia (serum sodium < 130 mmol/L); pre-existing hypotension (systolic blood pressure < 90 mm Hg); patients with unstable cardiac failure; renal impairment (serum creatinine > 150 micromol/litre); those on high-dose vasodilator therapy; patients aged 70 years or over (see 'Precautions').

Use in impaired renal function:
Excretion is primarily by the renal route. Enalapril Maleate should therefore be used with caution in patients with renal impairment. The recommended starting dose is 2.5 mg. The dose should be titrated against the response, and
should be kept as low as possible to maintain adequate control of blood pressure or heart failure.

Enalapril Maleate is dialysable. Dialysis patients may be given the usual dose of Enalapril Maleate on dialysis days. A high incidence of anaphylactoid reactions have been reported in patient dialysed with high-flux membranes and treated concomitantly with an ACE inhibitor. This combination should therefore be avoided. On the days when patients are not on dialysis the dosage should be tailored to the blood pressure response.

**Children:**
Not recommended. The paediatric use of Enalapril Maleate has not been studied.

### 4.3. Contra-indications

Enalapril Maleate is contra-indicated in pregnancy. When pregnancy is detected, treatment with Enalapril Maleate should be discontinued as soon as possible.

Hypersensitivity to the product or any of its components, and in patients with a history of angioneurotic oedema relating to previous treatment with an ACE inhibitor.

### 4.4. Special Warnings and Special 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 has been seen only rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Enalapril Maleate, 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 Dosage and administration for management of these patients.)

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 contra-indication 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. 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 may become necessary.

The appearance of hypotension after the initial dose of Enalapril Maleate does not preclude subsequent careful dose titration with the drug after effective management of the hypotension.

Impaired renal function: Enalapril Maleate should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses. Close monitoring of renal function before and during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

Renal failure has been reported in association with Enalapril Maleate and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with therapy with Enalapril Maleate is usually reversible.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when Enalapril Maleate has been given concurrently with a diuretic. Dosage reduction of Enalapril Maleate and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see 'Renovascular hypertension').

Renovascular hypertension: Enalapril Maleate can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients treated with diuretics and/or those with renal insufficiency.

Angioneurotic oedema has been reported with angiotensin-converting enzyme inhibitors, including Enalapril Maleate. This may occur at any time during treatment. In such cases, Enalapril Maleate should be discontinued immediately and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue,
glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5 mL 1:1000) should be administered promptly.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also 'Contra-indications').

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.

Haemodialysis patients: A high incidence of anaphylactoid reactions have been reported in patients dialysed with high-flux membranes and treated concomitantly with and ACE inhibitor. This combination should therefore be avoided.

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.

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 diagnoses of cough.

Surgery/anaesthesia: In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Enalapril Maleate blocks angiotensin-II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion.

General: Where Enalapril Maleate has been used as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

Enalapril Maleate should not be used in patients with aortic stenosis or outflow obstruction.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other Medicinal Products and other forms of Interaction
Combination with other antihypertensive agents such as beta-blockers, methyldopa, calcium antagonists, and diuretics may increase the antihypertensive efficacy of Enalapril Maleate. Adrenergic-blocking drugs should only be combined with Enalapril Maleate under careful supervision. Concomitant propranolol may reduce the bioavailability of Enalapril Maleate, but this does not appear to be of any clinical significance.

Concomitant therapy with lithium may increase the serum lithium concentration.

Plasma potassium usually remains within normal limits, although cases of hyperkalaemia have been reported. If Enalapril Maleate is given with a potassium-losing diuretic, the likelihood of diuretic-induced hypokalaemia may be lessened. Enalapril Maleate may elevate plasma potassium levels in patients with renal failure. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes are not recommended, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. However, if the concomitant use of these agents is deemed appropriate, they should be used with caution and with frequent monitoring of plasma potassium.

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 clinical trials with Enalapril Maleate have not confirmed these findings and do not preclude the use in diabetic patients. It is advised, however, that these patients be monitored.

Narcotic drugs/antipsychotics: postural hypotension may occur with ACE inhibitors.

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

Non-steroid anti-inflammatory drugs: the administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of an ACE inhibitor. However, in a clinical pharmacology study, indomethacin or sulindac was administered to hypertensive patients receiving Enalapril Maleate and there was no evidence of a blunting of the antihypertensive action of Enalapril Maleate. Furthermore, it has been described that NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function.

Antacids: induce decreased bioavailability of ACE inhibitors.
Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored, to confirm that the desired effect is being obtained.

Alcohol: enhances the hypotensive effect with ACE inhibitors.

Ciclosporin: increases the risk of hyperkalaemia with ACE inhibitors.

4.6. Pregnancy and Lactation

Enalapril Maleate has been shown to be foetotoxic in rabbits during middle and late pregnancy.

Foetal exposure in humans during the second and third trimesters of pregnancy has been associated with foetal and neonatal morbidity and mortality.

ACE inhibitors in human pregnancy have been associated with oligohydramnios which may result in limb contractures, craniofacial deformations and hypoplastic lung development. Hypotension, renal failure, hyperkalaemia and skull hypoplasia have occurred in the new-born. These adverse effects to the embryo and foetus do not appear to have resulted from intra-uterine ACE-inhibitor exposure limited to the first trimester.

Because of these findings, Enalapril Maleate is contraindicated in pregnancy. When pregnancy is detected, treatment with Enalapril Maleate should be discontinued as soon as possible.

Breast feeding mothers: Enalapril Maleate and Enalaprilat are excreted in human milk; caution should be exercised if Enalapril Maleate is given to breast-feeding mothers.

4.7. Effects on Ability to Drive and Use Machines

There is no data to suggest that Enalapril Maleate affects the ability to drive and use machines.

4.8. Undesirable Effects

Severe hypotension and renal failure have occurred in association with therapy with Enalapril Maleate. These appear to occur in certain specific sub-groups.

Other adverse reactions: Dizziness and headaches are the most commonly reported side effects. Less frequently, fatigue, asthenia, hypotension, orthostatic hypotension, syncope, nausea, diarrhoea, muscle cramps, rash, and cough have been reported. Even less frequently, renal dysfunction, renal failure, and oliguria have been reported.
Rarely reported side-effects include:

**Cardiovascular:** Myocardial infarction or cerebrovascular accident, possibly secondary to severe hypotension in high-risk patients (see 'Precautions'), chest pain, palpitations, rhythm disturbances, angina pectoris.

**Gastro-intestinal:** Ileus, pancreatitis, hepatic failure, hepatitis-either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

**Nervous system/Psychiatric:** Depression, confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo.

**Respiratory:** Pulmonary infiltrates, bronchospasm, asthma, dyspnoea, rhinorrhoea, sore throat and hoarseness.

**Skin:** Diaphoresis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus, pruritus, urticaria, alopecia.

**Other:** Impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision. A complex of symptoms has been reported which may include fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leucocytosis. Rash, photosensitivity or other dermatological manifestations may occur.

**Hypersensitivity/Angioneurotic oedema:** Angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported rarely (see 'Precautions').

**Laboratory test findings:** Increases in blood urea and plasma creatinine, reversible on discontinuation of Enalapril Maleate, are most likely in the presence of severe heart failure or bilateral renal artery stenosis, especially in patients with renal insufficiency (see 'Precautions'). However, increases in blood urea and plasma creatinine may occur without evidence of pre-existing renal impairment, especially in patients taking diuretics. In this event undiagnosed renal artery stenosis should be suspected. Dosage reduction of Enalapril Maleate and/or discontinuation of the diuretic should be considered.

**Hyperkalaemia and hyponatraemia** have also been reported in a few cases.

Decreases in haemoglobin and haematocrit as well as elevation of liver enzymes and/or serum bilirubin have been reported in a few patients, and are usually reversible upon discontinuation of Enalapril Maleate.

Decreases in platelets and white cell count, and rare cases of neutropenia, thrombocytopenia, bone marrow depression, and agranulocytosis have been reported, but a causal relationship to Enalapril Maleate has not been established.
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 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 Maleate, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If ingestion is recent, induce emesis. Enalapril Maleate can be removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Following oral administration, Enalapril Maleate is rapidly absorbed and hydrolysed to Enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin-converting enzyme inhibitor. Enalaprilat modulates a specific physiological mechanism, the renin-angiotensin-aldosterone system, which plays a major role in the regulation of blood pressure. Onset of action begins smoothly and gradually within one hour and the effects continue usually for 24 hours after a single daily dose.

Data indicate no loss of effect during long term therapy. Rebound hypertension does not occur following abrupt cessation of therapy.

Congestive heart failure patients benefit particularly from reduction in pre-load and after-load of the heart, with an increase in cardiac output, without reflex tachycardia.

5.2. Pharmacokinetic Properties

Following oral administration, peak serum concentrations occur within one hour. Based on urinary recovery, the extent of absorption is approximately 60%. The absorption of Enalapril Maleate is not affected by food. Peak serum concentrations occur three to four hours after an oral dose. Excretion is primary renal. Approximately 94% of the dose is recovered in the urine and faeces as Enalapril Maleate or Enalaprilat. Enalaprilat is 50% to 60% bound to plasma proteins, its elimination is multiphasic with a half life of 11 hours after multiple doses to patients with normal renal function.

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 Maleate does not have serious adverse effects on fertility and reproductive performance in rats, and it is not teratogenic. It crosses the placenta and has been shown to be foetotoxic in rabbits during middle and late pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipient(s)

croscarmellose sodium, lactose monohydrate, magnesium stearate, pregelatinised maize starch, sodium hydrogen carbonate
Red iron oxide (E172)
Yellow iron oxide (E172).

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

24 months

6.4. Special Precautions for Storage

Do not store above 25 ºC

6.5. Nature and Contents of Container

Al/Al blisters: Pack sizes 28 tablets
Securitainer: Pack sizes 50 tablets

6.6. Instruction for Use/Handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

CP Pharmaceuticals Limited
8. **MARKETING AUTHORISATION NUMBER**

PL 04543/0505

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

09/06/2006

10. **DATE OF REVISION OF THE TEXT**

09/06/2006
PATIENT INFORMATION LEAFLET
Enalapril Maleate 2.5, 5, 10 and 20 mg Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it onto others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What enalapril maleate is and what it is used for
2. Before you take enalapril maleate
3. How to take enalapril maleate
4. Possible side effect
5. Storing enalapril maleate

The active ingredient in Enalapril Maleate tablets is enalapril maleate. Each tablet contains 2.5, 5, 10 or 20 mg respectively of enalapril maleate.
The tablets also contain croscarmellose sodium, lactose monohydrate, magnesium stearate, maize starch, pregelatinised sodium bicarbonate and for 10 and 20 mg tablets only - iron oxides (E172).
Enalapril Maleate tablets are available in blister packs of 28 tablets or Securcontainers of 50 tablets (not all packs will be marketed).

Product Licence Holder:
CPharmaceuticals Limited, Ash Road North, Wrexham, LL13 9UF, UK
Manufacturer:
Actavis Limited, Reykjavíkurvegur 78, IS-102 Hafravatn, Iceland

1. WHAT ENALAPRIL MALEATE IS AND WHAT IT IS USED FOR

Enalapril maleate is one of a group of medicines called ACE (angiotensin converting enzyme) inhibitors. These medicines work by widening blood vessels which makes it easier for the heart to pump blood through them, to all parts of the body. This helps to reduce raised blood pressure. In many patients with heart failure, Enalapril maleate tablets will help your heart to work better.

Your doctor has probably prescribed enalapril maleate for you for one of the following reasons which will have been explained to you:
- 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 the ankles and legs.
- Enalapril may prevent heart failure from getting worse in some patients who have symptoms. These patients may be less likely to go into hospital for treatment of heart failure.
- In many patients with early stage heart failure who have no symptoms, including those who have had a heart attack, enalapril may help prevent your heart from weakening further (this is, to help prevent you from developing heart failure).
- By taking enalapril, some heart failure patients (with or without symptoms) may lessen their risk of heart attack.

2. BEFORE YOU TAKE ENALAPRIL MALEATE

It is important that you tell your doctor everything about your condition and of any problems you may have had in the past. Tell him if you have ever reacted badly to enalapril maleate.

If you answer YES to any of the following questions, or you are unsure, talk to your doctor or pharmacist BEFORE taking this medicine.
- Are you or do you think you may be pregnant?
- Are you planning to become pregnant?
- Are you breast-feeding?
- Have you suffered from a reaction to enalapril or similar medicines in the past, or to any of the ingredients and have experienced symptoms such as itching, rash, wheezing or swelling of the hands, throat, mouth or eyelids?
- Have you a condition called aortic stenosis or outflow obstruction?

If you have kidney disease or are a dialysis patient, check with your doctor before taking enalapril. In addition you should tell your doctor if you suffer from excessive vomiting or diarrhoea.
In addition to measuring your blood pressure your doctor may wish to test that your kidneys are working properly before you start taking the tablets and at intervals during your treatment.

If you undergo any surgery or receive anaesthetics (even at the dentist), you should make sure the doctor or dentist treating you is aware that you are taking enalapril.

If you are about to have a treatment called LDL apheresis, which is the removal of cholesterol from the body by machine, you should tell your doctor who is treating you that you are taking enalapril.

If you are about to have desensitisation treatment, that is treatment to reduce the effects of an allergy to bee or wasp stings, you should tell your doctor who is treating you that you are taking enalapril.

It is important to tell your doctor if you suffer from lactose intolerance. Lactose is one of the inactive ingredients in Enalapril Maleate tablets.

Taking enalapril maleate with other medicines:

If taken with some other medicines the effects of enalapril maleate or the effects of other medicines may be changed. Please check with your doctor if you are taking any of the following:

- Other medicines used to treat high blood pressure or heart failure such as:
  - Beta-blockers for example propranolol, bisoprolol, timolol, labetalol etc.
  - Calcium channel blockers for example nifedipine, diltiazem, verapamil etc.
  - Diuretics (water tablets) for example furosemide, hydrochlorothiazide, thiazide etc.
- Adrenergic nerve blocking medicines for example propranolol, guanethidine, propranolol, timolol etc.
- Various lithium salts used to treat depression for example lithium carbonate, lithium citrate etc.
- Medicines used to treat kidney problems
  - Potassium supplements or potassium containing salt substitutes for example potassium chloride, potassium carbonate, potassium citrate etc.
  - Diuretics (water tablets) that remove water but retain potassium from the body for example amiloride, triamterene, spironolactone, co-amilozide, co-amilofruse etc.
- Medicines for the treatment of diabetes (agents to lower blood sugar) for example insulin, chlorpropamide, gliclazide, gliclazide etc.
- Narcotics drugs for the treatment of moderate to severe pain, for example morphine, codeine, methadone, pethidine etc.
- Antidepressants used to treat the severe change of mood/mental disorders, for example lithium salts
- Medicines used to treat gout or gouty arthritis, for example colchicine.
- Immunosuppressive agents (suppress the body’s immune reactions) used in rheumatoid arthritis and used after organ transplant surgery, for example ciclosporin.
- Corticosteroids used mainly to treat various conditions including arthritis, allergic conditions, asthma, skin diseases for example hydrocortisone, prednisolone, beclometasone, dexamethasone, triamcinolone etc.
- Proton pump inhibitors used to treat irregular heart rhythm.
- Non-steroidal anti-inflammatory drugs (NSAIDs) used to relieve pain in muscles, bones and joints for example ibuprofen, diclofenac, ketoprofen etc.
- Antacids used for the relief of acid indigestion, for example Gaviscon, Milk of magnesia.
- Medicines sometimes taken for treatment of asthma and colds e.g. ephedrine, and phenylpropane.
- Any type of alcohol or alcoholic beverages.

It is also important that you tell your doctor about any medicines you are taking that you obtained without a prescription.

3. HOW TO TAKE ENALAPRIL MALEATE

You must keep taking enalapril as your doctor has told you. The dose you take will depend on your condition and whether you are taking any other treatment.

The usual dosages are as follows:

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

Heart failure: The usual recommended starting dose is 2.5mg a day, which is gradually increased up to 20mg a day, given either once daily or in 2 doses of 10mg according to your doctor’s advice.

With concurrent diuretic therapy: The recommended initial dose of enalapril is 2.5mg. If possible, your doctor will ask you to stop taking your diuretic tablets 2-3 days before starting to take your enalapril maleate tablets.

You should take your tablet at the same time each day unless your doctor tells you otherwise. If you are taking 2 tablets a day, take one in the morning and one in the evening, unless your doctor has told you otherwise.

If you are unsure or confused about what to do, talk to your doctor or pharmacist.

Drinking a moderate amount of alcohol may be acceptable when taking Enalapril Maleate Tablets but ask your doctor if drinking alcohol is safe for you.

You should still be able to drive while taking enalapril but do not drive if you feel light-headed, dizzy or tired. Ask your doctor for advice if you have these symptoms.

Ask your doctor how much exercise you should do. Too much exercise can make you feel faint, particularly in hot weather.
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 tablet to make up. If you take too many tablets by mistake contact your doctor IMMEDIATELY.

4. POSSIBLE SIDE EFFECTS

Like all medicines, enalapril may occasionally cause side effects in some patients.

In certain patients a severe drop in blood pressure and kidney problems can occur. If you experience severe dizziness it is very important that you stop taking enalapril immediately and see your doctor as soon as possible.

The most commonly reported side effects are dizziness and headaches.

Less frequently, patients may experience tiredness, loss of strength/feeling weak, a fall in blood pressure sometimes only when standing, loss of consciousness, feeling sick, diarrhoea, muscle cramps, rash or cough.

Kidney problems have also been reported including the passing of less urine.

Rarely reported side effects after taking enalapril are as follows:-

Heart and the blood system
There have been reports of heart attacks in patients taking enalapril, particularly in those patients who suffer from extremely low blood pressure. Chest pain, a rapid heart beat, irregular heart beat, and feeling of straining pain in the chest have also been reported.

Stomach
Problems with the bowel muscles probably resulting in lower stomach pain, swelling of the pancreas, liver problems including hepatitis, stomach pain, being sick, heartburn, difficulty in digestion, constipation, loss of appetite, mouth ulcers.

Nervous system
General depression, confusion, sleepiness, inability to fall asleep, nervousness, feeling of numbness and tingling sensation, vertigo.

Breathing and Lungs
Problems with the lungs which may cause a feeling of shortness of breath or wheezing, asthma, feeling of an obstruction in the throat which affects breathing, runny nose, sore throat and hoarseness.

Skin
Excessive sweating, severe skin rash with possible swelling, itching, skin rash and hair loss.

Other general side effects
Sexual inability in men, flushing, taste alteration, ringing in the ears, swelling of the tongue, blurred vision. Patients have rarely reported a group of symptoms which include fever, swelling of the blood vessels, muscle pain and muscle inflammation, joint pain, arthritis and changes in the blood. Rash and increased sensitivity to sun light have been reported as well as other skin complications.

Allergic Reactions
Swelling of the face, extremities (fingers, toes etc.), lips, tongue, throat/vocal box / vocal cords

If you are concerned about any of these effects or get any other unusual effects, tell your doctor immediately. Please do not be worried, most people taking this medicine will not experience any problems.

5. STORING ENALAPRIL MALEATE TABLETS

Keep your tablets out of the reach and sight of children.

Bottle: Do not store above 25°C. Store in the original packaging.

Do not use this medicine after the expiry date shown on the carton.

Return any unused tablets to your pharmacist for safe disposal.

The leaflet was prepared in March 2005.

CP Pharmaceuticals Limited Wrexham UK
LABELLING

Blister

2.5mg:

5mg:
10mg:

MHRA PAR Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg Tablets, PL 04543/0503-05 & 0514

20mg:

MHRA PAR Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg Tablets, PL 04543/0503-05 & 0514
Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg Tablets, PL 04543/05, 03-05 & 0514

Bottle label
Braille to be inserted on the front panel reads: Enalapril 5mg Tablets
Braille to be inserted on the front panel reads: Enalapril 10mg Tablets

Patient Pack
X Tablets
Dose: As directed by the physician, also contains lactose, see leaflet for further information.
Do not store above 25°C.
Keep out of the reach and sight of children.
Please read Patient Information Leaflet before use.
CP Pharmaceuticals Ltd, Ash Road North, Wrexham, LL13 9UF, UK. PL 04543/0503 POM

10mg Tablets
Each tablet contains 10mg of enalapril maleate
For oral use

© CP Pharmaceuticals Ltd Wrexham UK
20mg Enalapril Maleate 2.5mg, 5mg, 10mg and 20mg Tablets, PL 04543/0050-0-03-05 & 0514

Patient Pack
X Tablets

Dose: As directed by the physician.
Also contains lactose, see leaflet for further information.
Do not store above 25°C.
Keep out of the reach and sight of children.
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CP Pharmaceuticals Ltd, Ash Road North,
Wrexham, LL13 9UF, UK  PL 04543/0505  POM

Braille to be inserted on the front panel
reads: Enalapril 20mg Tablets

20mg Tablets
Each tablet contains 20mg of enalapril maleate
For oral use

CP Pharmaceuticals Ltd Wrexham UK
Carton label

2.5mg:
5mg:

Enalapril Maleate 5mg Tablets Carton
Version C Mockup 24/03/06
Amended 22/05/09
Colour: Blue 201, Warm Red
Size: 52 x 25.127mm
10mg:
20mg: