

SUMMARY OF PRODUCT CHARACTERISTICS

NOTE:

THIS SPC IS THE ONE THAT WAS ANNEXED TO THE COMMISSION DECISION CONCERNING THIS REFERRAL; THE TEXT WAS VALID AT THAT TIME.

IT IS NOT SUBSEQUENTLY MAINTAINED OR UPDATED BY THE EMEA, AND THEREFORE MAY NOT NECESSARILY REPRESENT THE CURRENT TEXT.

1. NAME OF THE MEDICINAL PRODUCT

<Renitec and associated names (see Annex I)>, <strength>, tablets.
[To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains <strength> mg enalapril maleate.
[To be implemented nationally]

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of Hypertension.
- Treatment of Symptomatic Heart Failure.
- Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction $\leq 35\%$).

(See Section 5.1 Pharmacodynamic properties.)

4.2 Posology and method of administration

The absorption of <Renitec> is not affected by food.

The dose should be individualized according to patient profile (see 4.4 Special warnings and special precautions for use) and blood pressure response.

Hypertension

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

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

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

Heart Failure/Asymptomatic Left Ventricular Dysfunction

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

Suggested Dosage Titration of <Renitec> in Patients with Heart Failure/Asymptomatic Left Ventricular Dysfunction

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

*Special precautions should be followed in patients with impaired renal function or taking diuretics (See 4.4 Special warnings and special precautions for use).

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

Dosage in Renal Insufficiency

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

Creatinine Clearance (CrCL) mL/min	Initial Dose mg/day
30 < CrCL < 80 ml/min.	5 - 10 mg
10 < CrCL ≤ 30 ml/min.	2.5 mg
CrCL ≤ 10 ml/min.	2.5 mg on dialysis days*

* See 4.4 Special warnings and special precautions for use - Hemodialysis Patients. Enalaprilat is dialyzable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

Use in Elderly

The dose should be in line with the renal function of the elderly patient (see 4.4 Special warnings and special precautions for use, Renal Function Impairment).

Use in paediatrics

There is limited clinical trial experience of the use of <Renitec> in hypertensive paediatric patients (see 4.4 Special warnings and special precautions for use, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

For patients who can swallow tablets, the dose should be individualized according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥ 50 kg. <Renitec> is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥ 50 kg. (See 4.4 Special warnings and special precautions for use.)

<Renitec> is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Symptomatic Hypotension

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving <Renitec>, symptomatic hypotension is more likely to occur if the patient has been volume - depleted, e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting (see 4.5 Interaction with other medicaments and other forms of interaction and 4.8 Side Effects). 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, hyponatremia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of <Renitec> and/or diuretic is adjusted. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

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

Aortic or Mitral Valve Stenosis/Hypertrophic Cardiomyopathy

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

Renal Function Impairment

In cases of renal impairment (creatinine clearance <80 ml/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance (see 4.2 Posology and method of administration) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If recognized 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 4.4 Special warnings and special precautions for use, Renovascular hypertension).

Renovascular hypertension

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

Kidney Transplantation

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

Hepatic failure

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

Neutropenia/Agranulocytosis

Neutropenia/agranulocytosis, thrombocytopenia and anemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Enalapril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections which in a few instances did not respond to intensive antibiotic therapy. If enalapril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

Hypersensitivity/Angioneurotic Edema

Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including <Renitec>. This may occur at any time during treatment. In such cases, <Renitec> should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioneurotic edema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

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

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (Also see 4.3 Contraindications.)

Anaphylactoid Reactions during Hymenoptera Desensitization

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

Anaphylactoid Reactions during LDL Apheresis

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

Hemodialysis Patients

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

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (See 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia

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

Hyperkalemia

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

Lithium

The combination of lithium and enalapril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lactose

<Renitec> contains less than 200 mg of lactose per tablet.

Paediatric Use

There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see 4.2 Posology and method of administration, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties.) <Renitec> is not recommended in children in other indications than hypertension.

<Renitec> is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m², as no data are available. (See 4.2 Posology and method of administration.)

Pregnancy and lactation

Enalapril should not be used during the first trimester of pregnancy. <Renitec> is contraindicated in the second and third trimesters of pregnancy (see 4.3 Contraindications). When pregnancy is detected, enalapril treatment should be discontinued as soon as possible (see 4.6 Pregnancy and lactation).

Use of enalapril is not recommended during breast feeding.

Ethnic differences

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

4.5 Interaction with other medicinal products and other forms of interaction

Potassium sparing diuretics or potassium supplements

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

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see 4.4 Special warnings and special precautions for use). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

Other antihypertensive agents

Concomitant use of these agents may increase the hypotensive effects of enalapril. Concomitant use with nitroglycerine and other nitrates, or other vasodilators, may further reduce blood pressure.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of enalapril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see 4.4 Special warnings and special precautions for use).

Tricyclic antidepressants/Antipsychotics/Anesthetics/Narcotics

Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see 4.4 Special warnings and special precautions for use).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

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

Alcohol

Alcohol enhances the hypotensive effect of ACE inhibitors.

Acetyl salicylic acid, thrombolytics and β -blockers

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

4.6 Pregnancy and lactation

Pregnancy

Enalapril should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester exposure have not appeared to manifest malformations consistent with human fetotoxicity as described below.

Enalapril is contraindicated during the second and third trimesters of pregnancy.

Prolonged enalapril exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). (Also see 5.3 Preclinical safety data.)

Should exposure to enalapril have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken <Renitec> should be closely observed for hypotension, oliguria and hyperkalemia. Enalapril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation

Enalapril and enalaprilat are excreted in breast milk but their effect on the nursing infant has not been determined. Consequently, use of enalapril is not recommended if breast-feeding.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Undesirable effects reported for enalapril include:

Blood and the lymphatic system disorders:

uncommon: anemia (including aplastic and hemolytic)

rare: neutropenia, decreases in hemoglobin, decreases in hematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases

Metabolism and nutrition disorders:

uncommon: hypoglycemia (see 4.4 Special warnings and special precautions for use, Diabetic patients)

Nervous system and psychiatric disorders:

common: headache, depression

uncommon: confusion, somnolence, insomnia, nervousness, paresthesia, vertigo

rare: dream abnormality, sleep disorders

Eye disorders:

very common: blurred vision

Cardiac and vascular disorders:

very common: dizziness

common: hypotension (including orthostatic hypotension), syncope, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see 4.4 Special warnings and special precautions for use), chest pain, rhythm disturbances, angina pectoris, tachycardia

uncommon: orthostatic hypotension, palpitations

rare: Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

very common: cough

common: dyspnea

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

rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:

very common: nausea,

common: diarrhea, abdominal pain, taste alteration

uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer

rare: stomatitis/aphthous ulcerations, glossitis

Hepatobiliary disorders:

rare: hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)

Skin and subcutaneous tissue disorders:

common: rash, hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see 4.4 Special warnings and special precautions for use)

uncommon: diaphoresis, pruritus, urticaria, alopecia

rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma

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

Renal and urinary disorders:

uncommon: renal dysfunction, renal failure, proteinuria

rare: oliguria

Reproductive system and breast disorders:

uncommon: impotence

rare: gynecomastia

General disorders and administration site conditions:

very common: asthenia

common: fatigue

uncommon: muscle cramps, flushing, tinnitus, malaise, fever

Investigations:

common: hyperkalemia, increases in serum creatinine

uncommon: increases in blood urea, hyponatremia

rare: elevations of liver enzymes, elevations of serum bilirubin

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

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by hemodialysis. (See 4.4 Special warnings and special precautions for use, Hemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC Code: C09A A02

<Renitec>(enalapril maleate) is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolyzed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

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

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

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

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

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

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

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

When given together with thiazide-type diuretics, the blood pressure-lowering effects of <Renitec> are at least additive. <Renitec> may reduce or prevent the development of thiazide-induced hypokalemia.

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

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

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

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

the risk of myocardial infarction by 23% (95% CI, 11 – 34%; p<0.001) and reduced the risk of hospitalization for unstable angina pectoris by 20% (95% CI, 9 – 29%; p<0.001).

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

5.2 Pharmacokinetic properties

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

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

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

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

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

Renal impairment

The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 ml/min) steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤ 30 ml/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed. (See 4.2 Posology and method of administration.) Enalaprilat may be removed from the general circulation by hemodialysis. The dialysis clearance is 62 ml/min.

Children and adolescents

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

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The compound has been shown to cross the placenta and is secreted in milk. Angiotensin converting enzyme inhibitors, as a class, have been shown to be fetotoxic (causing injury and/or death to the fetus) when given in the second or third trimester.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be implemented nationally]

6.2 Incompatibilities

[To be implemented nationally]

6.3 Shelf life

[To be implemented nationally]

6.4 Special precautions for storage

[To be implemented nationally]

6.5 Nature and contents of container

[See Annex I - to be implemented nationally]

6.6 Instructions for use and handling

[To be implemented nationally]

7. MARKETING AUTHORIZATION HOLDER

[See Annex I -to be implemented nationally]

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT