Enalapril maleate

Core Safety Profile

4.2 Posology and method of administration

The absorption of Tablets RENITEC is not affected by food.

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

Hypertension The initial dose is 5 to maximally 20 mg, depending on the degree of hypertension and the condition of the patient (see below). RENITEC is given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg. Patients with a strongly activated renin-angiotensinaldosterone 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 section 4.4).

Blood pressure and renal function should be monitored closely both before and after starting treatment with RENITEC (see section 4.4) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with 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 section 4.4
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 section 4.4).

Use in pediatrics There is limited clinical trial experience of the use of RENITEC in hypertensive pediatric patients (see sections 4.4, 5.1 and 5.2).

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 section 4.4.)

RENITEC is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available.

4.3 Contraindications

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

4.4 Special warnings and 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 sections 4.5 and 4.8). 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 hemodynamically significant obstruction.

Renal Function Impairment In cases of renal impairment (creatinine clearance <80 ml/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients. Renal failure has been reported in association with enalapril and has been mainly in patients with severe heart failure or underlying renal disease, including renal artery stenosis. If 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 section 4.4, Renovascular hypertension).

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

Kidney Transplantation There is no experience regarding the administration of 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 or hepatitis and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

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

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

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

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

Anaphylactoid Reactions during LDL Apheresis Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran 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.

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

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. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of enalapril and any of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium. (See section 4.5)

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

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

Pediatric Use There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see sections 4.2, 5.1, and 5.2) RENITEC is not recommended in children in other indications than hypertension. RENITEC is not recommended in neonates and in pediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available. (See section 4.2.)

Pregnancy and lactation Ace inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).
Use of enalapril is not recommended during breast feeding (see sections 4.6 and 5.2).

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, eplerenone, 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 section 4.4).

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

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 section 4.4).

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 section 4.4).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

NSAIDs (including COX-2 inhibitors) 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 patients who are volume-depleted, including those on diuretic therapy). Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Gold Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including enalapril.

Sympathomimetics Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased bloodglucose-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. (See sections 4.4 and 4.8)

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

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitors therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

ACE inhibitors therapy exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). (See section 5.3). Should exposure to ACE inhibitors have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant the use of RENITEC in breast-feeding is not recommended for preterm infants and for the first few weeks after delivery,

because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience. In case of an older infant the use of RENITEC in breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Undesirable effects reported for enalapril include:

Very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders:

uncommon: anemia (including aplastic and hemolytic)

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

Endocrine disorders:

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

Metabolism and nutrition disorders:

uncommon: hypoglycemia (see section 4.4)

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, chest pain, rhythm disturbances, angina pectoris, tachycardia uncommon: orthostatic hypotension, palpitations, myocardial infarction or cerebrovascular accident*, possibly secondary to excessive hypotension in high risk patients (see section 4.4)
rare: Raynaud's phenomenon

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, very rare: intestinal angioedema

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

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

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

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

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

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 section 4.4.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.