RENITEC®

(enalapril maleate, MSD)

COMPOSITION

RENITEC contains per tablet 5, 10 or 20 mg of enalapril maleate.

PROPERTIES

Tablets RENITEC contain the maleate salt of enalapril, a derivative of two amino acids, L-alanine and L-proline. Following oral administration, enalapril is rapidly absorbed and then hydrolyzed to enalaprilat, which is a highly specific, long-acting, nonsulphydryl angiotensin converting enzyme inhibitor.
Enalapril lowers blood pressure in patients with hypertension and improves the signs and symptoms in patients with chronic congestive heart failure.

Mechanism of action

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 inhibition of negative feedback of renin release) and decreased aldosterone secretion.
ACE is identical to kininase II. Thus enalapril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of enalapril remains to be elucidated.
While the mechanism through which enalapril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, enalapril may have an antihypertensive effect even in patients with low-renin hypertension.

Protein binding

Enalaprilat binding to human plasma indicates the presence of two binding sites. One is a high affinity, low capacity site which predominates at enalaprilat concentrations less than 8 ng/ml. This high affinity binding appears to be due to plasma ACE. The other has greater capacity and lower affinity but, over the range of concentrations which are therapeutically relevant, binding does not exceed 60 % suggesting that it is not of importance with regard to the pharmacokinetics of the drug.

Pharmacokinetics and metabolism

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of oral enalapril is approximately 60 % - 70 %.
Following absorption, oral enalapril is rapidly and largely hydrolyzed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur 3 to 4 hours after an oral dose of RENITEC. Excretion of enalapril is primarily renal. The principal components in urine are enalaprilat, accounting for about 40 % of the dose, and intact enalapril. Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril. The serum concentration profile of enalaprilat exhibits a prolonged terminal phase, apparently associated with binding of ACE. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of RENITEC once daily. The effective half-life for accumulation of enalaprilat following multiple oral doses of RENITEC is 11 hours. The absorption of enalapril is not influenced by the presence of food in the gastrointestinal tract. The extent of absorption and hydrolysis of enalapril are similar for the various doses in the recommended therapeutic range. In cirrhotic patients the hydrolysis of enalapril to its active metabolite may be retarded.

Pharmacodynamics

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 short term clinical studies in diabetic and nondiabetic patients with renal disease and proteinuria, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.
In patients with essential hypertension, blood pressure reduction is usually 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 is usually an increase in renal blood flow; glomerular filtration rate is usually unchanged.
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 congestive heart failure on therapy with digitalis and diuretics, treatment with enalapril is usually associated with the following: decreased peripheral resistance and blood pressure; increased cardiac output, while heart rate (usually elevated in patients with congestive heart failure) decreases; reduced pulmonary capillary wedge pressure; improvement in exercise tolerance and severity of congestive heart failure, as measured by New York Heart Association criteria. These actions continue during chronic therapy.
Clinical data have shown that enalapril reduced the frequency of ventricular arrhythmias in patients with congestive heart failure. The underlying mechanisms and clinical significance are not known. An increase in serum potassium at low initial values seems to play an important role.
In a multi-center, placebo-controlled, double-blind study involving 253 patients with severe congestive heart failure (New York Heart Association class IV), RENITEC, as an adjunct to conventional therapy, was shown to significantly improve symptoms and reduce mortality.

INDICATIONS

- essential hypertension
- renovascular hypertension
- symptomatic improvement of congestive heart failure and reduction of mortality in patients with severe heart failure.

CONTRAINDICATIONS

RENITEC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioneurotic edema, either relating to previous treatment with an angiotensin-converting enzyme inhibitor or not.

SIDE-EFFECTS

The following side-effects have been associated with the use of RENITEC:
Dizziness and headache were the more commonly reported side-effects. Fatigue and asthenia were reported in 2 - 3 % of patients. Other side-effects occurred in less than 2 % of patients, and included hypotension, orthostatic hypotension, syncope, nausea, diarrhea, muscle cramps, rash, and cough. Less frequently renal dysfunction, renal failure, and oliguria have been reported.

Hypersensitivity/Angioneurotic Edema

Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in individual patients (see Warnings and Precautions).
Side-effects which occured very rarely, either during controlled clinical trials or after the drug was marketed, include:

Cardiovascular

Myocardial infarction of cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see Precautions), chest pain, palpitations, rhythm disturbances, angina pectoris.

Gastrointestinal

Ileus, pancreatitis, hepatitis either hepatocellular or cholestatic, jaundice, abdominal pain, vomiting, dyspepsia, constipation, anorexia, stomatitis.

Nervous system/psychiatric

Depression, confusion, somnolence, insomnia, nervousness, paresthesia, vertigo.

Respiratory

Bronchospasm, dyspnea, rhinorrhea, sore throat and hoarseness.

Skin

Diaphoresis, erythma multiforme, exfoliative dermatitis, Stevens Johnson syndrome, toxic epidermal necrolysis, pruritus, urticaria, alopecia.

Other

Impotence, flushing, taste alteration, tinnitus, glossitis, blurred vision.
A symptom complex has been reported which may include fever, serositis, vasculitis, myalgia and arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Laboratory test findings

In patients with renal failure the administration of RENITEC may lead to elevation of serum potassium (see Warnings and Precautions). Increases in blood urea and serum creatinine and elevations of liver enzymes and/or serum bilirubin have been seen. These are usually reversible upon discontinuation of RENITEC. Hyperkalemia and hyponatremia have occurred.
Decreases in hemoglobin and hematocrit have been reported.
Since the drug was marketed a small number of cases of neutropenia, thrombocytopenia, bone marrow depression and agranulocytosis have been reported, but a causal relationship to therapy with RENITEC could not be excluded.

WARNINGS AND PRECAUTIONS

Symptomatic hypotension

Symptomatic hypotension may occur sometimes after the first dose of RENITEC. In hypertensive patients receiving RENITEC, 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 Drug interactions and Side-effects). In patients with congestive heart failure, with or without associated renal insufficiency, there is an increased risk of symptomatic hypotension. 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 diuretics, hyponatremia or functional renal impairment. In these patients, therapy should be started in a hospital 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 congestive 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 or discontinuation of RENITEC may be necessary.

Alertness is required for patients with aortic stenosis on account of the potential risk of reduced coronary and cerebral blood flow due to the diminished blood pressure.

Impaired renal function

Since enalapril and enalaprilat are almost completely excreted by the kidney, patients with renal insufficiency require reduced and/or less frequent doses of RENITEC (see Dosage) and their renal function should be monitored. In the majority, renal function will not alter, and in some it may improve. In patients with renal failure the administration of RENITEC may lead to elevation of serum potassium.

Acute deterioration of renal function may however occur, especially in patients with impaired renal function, congestive heart failure, and renovascular hypertension, in particular when there is bilateral renal artery stenosis or unilateral stenosis with only one functioning kidney, such as following renal transplantation. Treatment whith diuretics may be a contributory factor. This deterioration is usually reversible after reduction of dosage or withdrawal of enalapril. In these groups of patients it is preferable to continue monitoring renal function following institution of treatment. Allowance should also be made for the fact that unilateral renal artery stenosis with two functioning kidneys may also be associated with acute reversible failure of the function of the effected kidney without serious deterioration of renal function. In this case renography is indicated unless surgical intervention is undertaken at short notice (one month).

Hypersensitivity/angioneurotic edema

Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in individual patients treated with angiotensin converting enzyme inhibitors, including RENITEC. 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 such as subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) 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. (Also see Contraindications).

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.

Pediatric use

RENITEC has not been studied in children.

EFFECT ON THE ABILITY TO DRIVE AND TO OPERATE MACHINERY

No data are known about the effect on the ability to drive. In connection with the possible occurrence of dizziness a negative effect on the ability to drive and to operate machinery should be taken into account.

USE IN PREGNANCY AND DURING LACTATION

There are no adequate and well-controlled studies of enalapril in pregnant women. However, clinical observations indicate that ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women; therefore, the use of RENITEC during pregnancy is not recommended unless needed in a situation where other drugs cannot be used or are ineffective. If RENITEC is used, the patient should be apprised of the potential hazard to the fetus.

Enalaprilat crosses the human placenta. Infants whose mothers have taken RENITEC should be closely observed. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome. However, there have been reports of hypotension, renal failure, hyperkalemia, and/or skull hypoplasia in the newborn when ACE inhibitors were used during the second and third trimesters of pregnancy. Maternal oligohydramnios, presumably representing decreased renal function in the fetus, has occurred and may result in limb contractures and craniofacial deformations. If oligohydramnios is observed, RENITEC should be discontinued.

Enalaprilat has been removed from the neonatal circulation by peritoneal dialysis and theoretically may be removed by exchange dialysis, although there is no experience with the later procedure.

Enalapril and enalaprilat are secreted in human milk in trace amounts. Caution should be exercised if RENITEC is given to a nursing mother.

INTERACTIONS

Antihypertensive therapy

The combination of RENITEC with other antihypertensive drugs may increase the antihypertensive effect, especially in combination with diuretics.

The combination of RENITEC with betaadrenegic blocking agents and methyldopa improves the efficacy of lowering the blood pressure Propranolol coadministered with enalapril maleate reduces serum enalaprilat concentrations, but this does not seem to be of any clinical significance. Also a slight increase of the bioavailability of propranolol occurs. Ganglionic blocking agents and adrenergic blocking agents (such as guanethidene and reserpine), combined with RENITEC should only be administered under careful observation of the patient.

Serumpotassium

Serum potassium usually remains within normal limits. In patients treated with RENITEC plus a thiazide diuretic, there was essentially no change in serum potassium.

If RENITEC is given with a potassiumlosing diuretic, diuretic-induced hypokalemia may be ameliorated. The use of potassium supplements, potassium-containing salt substitutes or potassium-sparing diuretics in particular in patients with impaired renal function may lead to significant increase in serum potassium. If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Lithium

As with other drugs which eliminate sodium the lithium elimination may be reduced. Therefore the lithium levels of serum should carefully be compared if lithium salts are to be administered.

DOSAGE AND METHOD OF ADMINISTRATION

Oral

Since its absorption is not affected by food, RENITEC may be administered before, during or after meals.

The usual daily dosage ranges from 10 to 40 mg in all indications. RENITEC may be administered once or twice a day. In patients with essential hypertension with signs of volume and/or salt depletion, in patients with renovascular hypertension and in patients with congestive heart failure, a lower initial dose is necessary (see Warnings and Precautions and below). To date the maximum dose studied in man is 80 mg daily. In some patients a reduction of the effect may occur in the course of 24 hours with single daily dosage.

Essential hypertension

The initial dose is 10 to 20 mg daily depending on the degree of hypertension. In mild hypertension the recommended initial dose is 10 mg daily. For other degrees of hypertension the initial dose is 20 mg daily. The usual maintenance dose is 20 mg daily. The dosage should be adjusted according to the needs of the patient.

Renovascular Hypertension

Since blood pressure and renal function in such patients may be particularly sensitive to ACE inhibition, therapy should be initiated with a lower starting dose (e.g. 5 mg or less). The dosage should then be adjusted according to the needs of the patient. Most patients may be expected to respond to one 20 mg tablet taken once daily. For patients with hypertension who have been treated recently with diuretics, caution is recommended. (See next paragraph).

Concomitant Diuretic Therapy in Hypertension

Symptomatic hypotension may occur following the initial dose of RENITEC; this is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume or salt depleted. The diuretic therapy should be discontinued for 2 – 3 days prior to initiation of therapy with RENITEC. Also the initial dose of RENITEC should be low (5 mg or in case of serious volume and/or salt depletion 2.5 mg) to determine the initial effect on the blood pressure. Dosage should then be adjusted according to the needs of the patient.

Dosage in renal insufficiency

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

Renal status	creatinine-clearance ml/min	initial dose mg/day
Mild impairment	30-80 ml/min	5-10 mg
Moderate impairment	10-30 ml/min	2.5-5 mg
Severe impairment	< 10 ml/min	2.5 mg on dialysis days*
Normally, these patients will be on dialysis		

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

Congestive Heart Failure

Blood pressure and renal function should be monitored closely both before and after starting treatment with RENITEC (see Warnings and Precautions) because hypotension and (more rarely) consequent renal failure have been reported.

In patients with congestive heart failure, the usual maintenance dose is 10 to 20 mg daily, given in single or divided doses. The initial dose in patients with congestive heart failure in general amounts to 5 mg. In severe types, in particular in patients with impaired renal function, receiving potent diuretic therapy, and with hyponatremia, the initial dose should be 2.5 mg. Administration of diuretics should be briefly discontinued if possible. 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.

In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with RENITEC in congestive heart failure, the dose should be gradually increased, depending on the patient's response, to the usual maintenance dose (10 - 20 mg) given in a single or divided dose. This dose titration may be performed over a 2 to 4 week period, or more rapidly if indicated by the presence of residual signs and symptoms of heart failure.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available for overdosage in humans. The most prominent feature of overdosage reported to date is 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, respectively.

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

MSD