

RENITEC® I.V.
(enalaprilat)

Injection

SPECIALTY FOR HOSPITAL USE

RENITEC® I.V. (enalaprilat) is a sterile aqueous solution for intravenous administration. Enalaprilat is a derivative of two amino-acids, L-alanine and L-proline and is a highly specific, long-acting, non-sulfhydryl angiotensin converting enzyme inhibitor.

RENITEC is indicated in the treatment of all grades of essential hypertension. It may be used alone as initial therapy or concomitantly with other antihypertensive agents, especially diuretics.

RENITEC is also indicated in the treatment of heart failure.

RENITEC I.V. should be used only in those cases when the oral formulation is inadequate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 1 ml of RENITEC I.V. contains:

Enalaprilat (INN) (dihydrate)	1 mg
Excipient (see 6.1) q.s.	1 ml

3. PHARMACEUTICAL FORM

Solution for I.V. injection

4. CLINICAL DATA

4.1 Therapeutic Indications

Treatment of:

- * All grades of essential hypertension
- * Congestive heart failure

4.2 Dosage and Administration

Intravenous only

Onset of action commences within a few minutes after dosing. Maximum effect on blood pressure and hemodynamic parameters is usually seen within four hours. Studies involving

intravenous treatment beyond seven days have not been conducted. In other studies with hypertensive patients, RENITEC I.V. was not administered for periods longer than 48 hours.

Hypertension

The recommended starting dose of RENITEC I.V. for hypertension is 1 mg, administered intravenously over a period of not less than 5 minutes.

If after one hour the clinical response is inadequate, a further 1 or 2 mg dose may be given intravenously over 5 minutes. Further dosage adjustment, and subsequent maintenance dosage should be at 6-hour intervals.

When the patient is transferred from Injection RENITEC to Tablets RENITEC the initial dosage of Tablets RENITEC should be 5-10 mg once or twice a day.

Heart Failure

Regardless of previous oral administration, the recommended starting dose of RENITEC I.V. for heart failure is 0.5 mg, administered intravenously over a period of not less than 5 minutes and preferably over 1 hour with frequent monitoring of blood pressure.

If the clinical response is inadequate after one hour, a further 0.5 or 1 mg dose may be given intravenously in the same manner. Further dosage adjustment, and subsequent maintenance dosage should be at 6-hour intervals.

When the patient is transferred from Injection RENITEC to Tablets RENITEC the initial dosage of Tablets RENITEC should be 2.5-5 mg once or twice a day.

Hypertensive Patients With Renal Impairment

The recommended starting dose of RENITEC I.V. for patients with renal impairment is 0.5 mg, administered intravenously over a period of not less than 5 minutes.

If after one hour the clinical response is inadequate, a further 0.5 or 1 mg dose may be given intravenously over 5 minutes. Further dosage adjustment, and subsequent maintenance dosage should be at 6-hour intervals.

When the patient is transferred from Injection RENITEC to Tablets RENITEC the initial dosage of Tablets RENITEC should be 2.5 (if creatinine clearance is \leq 30 ml/min) and 5 mg (if creatinine clearance is $>$ 30 ml/min), once a day. The dosage should be adjusted according to the blood pressure response.

Hypertensive Patients Requiring Special Treatment

These include patients on diuretic therapy and patients with renovascular hypertension.

The recommended starting dose of RENITEC I.V. for these patients is 0.5 mg, administered intravenously over a period of not less than 5 minutes.

If after one hour the clinical response is inadequate, a further 0.5 mg dose may be given intravenously over 5 minutes. Further dosage adjustment, and subsequent maintenance dosage should be at 6-hour intervals.

When the patient is transferred from Injection RENITEC to Tablets RENITEC the initial daily dosage of Tablets RENITEC should be 2.5 mg once a day, adjusting the dose subsequently, if necessary.

DOSAGE AND ADMINISTRATION OF RENITEC I.V.

HYPERTENSION				
	ESSENTIAL	RENAL IMPAIRMENT	SPECIAL GROUPS	HEART FAILURE
INITIAL DOSE*	1mg over 5 min	0.5 mg over 5 min	0.5 mg over 5 min	0.5mg over 5-60 min
DOSAGE INTERVAL	every 6 hrs	every 6 hours	every 6 hours	every 6 hours
MAXIMUM DOSAGE	5 mg/ single dose	2 mg/ single dose	5 mg/ single dose	2 mg/ single dose
	20 mg/day	10 mg/day	20 mg/day	10 mg/day

*If clinical response is inadequate, the initial dose may be repeated or doubled at one hour. Further dosage adjustment may be necessary at 6 hourly intervals until the desired antihypertensive effect is obtained.

Administration

It is particularly important to administer each dose over at least 5 minutes, and preferably over 1 hour with frequent monitoring of blood pressure in the case of heart failure, so that any undesired response (e.g. hypotension) can be controlled at the earliest possible moment.

RENITEC I.V. may be administered as provided, or diluted with a compatible diluent.

Compatibility and Stability

Injection RENITEC as supplied, and mixed with the following intravenous diluents, has been found to maintain full activity for 24 hours at room temperature.

- 5 percent Dextrose Injection
- 0.9 percent Sodium Chloride Injection
- 0.9 percent Sodium Chloride Injection in 5 percent Dextrose
- 5 percent Dextrose in Ringer-Lactate solution

4.3 Contraindications

RENITEC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioneurotic edema relating to previous treatment with an angiotensin-converting enzyme inhibitor.

RENITEC has not been studied in children and is not indicated in children under 14 years of age.

4.4 Warnings and Special Precautions for Use

Symptomatic Hypotension

Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. 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 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.

Renal Function Impairment

In some patients hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

Patients with renal insufficiency may require reduced and/or less frequent doses of RENITEC (see Dosage and Administration). In some patients, with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and serum creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency.

Some patients with no apparent pre-existing renal disease, have developed usually minor and transient increases in blood urea and serum creatinine when RENITEC has been given concomitantly with a diuretic. Dosage reduction and/or discontinuation of the diuretic and/or RENITEC may be required.

Hypersensitivity/Angioneurotic Edema

Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including RENITEC. In such case, 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).

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.

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.

Serum Potassium - See Drug Interactions

Warning on excipients

Since this drug contains benzylic alcohol as an excipient, it is contraindicated in children under the age of three years.

4.5 **Interactions with Other Drugs and Other Forms of Interactions**

Antihypertensive Therapy

Additive effect may occur when RENITEC is used together with other antihypertensive therapy.

Serum Potassium

In clinical trials, serum potassium usually remained within normal limits. In hypertensive patients treated with RENITEC alone for up to 48 weeks, mean increases in serum potassium of approximately 0.2 mEq/L were observed. In patients treated with RENITEC plus a thiazide diuretic, the potassium-losing effect of the diuretic was attenuated usually by the effect of enalapril.

If RENITEC is given with a potassium-losing diuretic, diuretic-induced hypokalemia may be ameliorated.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes.

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.

If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium.

Serum Lithium

As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

4.6 **Pregnancy and Nursing**

Use in Pregnancy

The use of RENITEC during pregnancy is not recommended. When pregnancy is detected, RENITEC should be discontinued as soon as possible, unless it is considered life-saving for the mother.

ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women during the second and third trimesters. Use of ACE inhibitors during this period has been associated with fetal and neonatal injury including hypotension, renal failure, hyperkalemia, and/or skull hypoplasia in the newborn. Maternal oligohydramnios, presumably representing decreased fetal renal function, has occurred and may result in limb contractures, craniofacial deformations and hypoplastic lung development. If RENITEC is used, the patient should be apprised of the potential hazard to the fetus.

These adverse effects to the embryo and fetus do not appear to have resulted from intrauterine ACE-inhibitor exposure limited to the first trimester.

In those rare cases where ACE inhibitor use during pregnancy is deemed essential, serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is detected, RENITEC should be discontinued unless it is considered life-saving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

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.

Nursing Mothers

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

4.7 **Effect on the Capacity to Drive Automobiles and Use Machinery**

The same as with enalapril, with enalaprilat symptoms of hypotension and a sense of instability may appear at the beginning of treatment.

4.8 **Side Effects**

RENITEC has been demonstrated to be generally well tolerated. In clinical studies, the side effects, for the most part, have been mild and transient in nature, and have not required discontinuation of therapy.

The following side effects have been associated with the use of Tablets and Injection 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.

Symptomatic hypotension occurred more frequently with Injection RENITEC than with Tablets RENITEC.

Hypersensitivity/Angioneurotic Edema

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

Side effects which occurred very rarely, either during controlled clinical trials or after the drug was marketed, include:

Cardiovascular

myocardial infarction or 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/asthma
dyspnea
rhinorrhea
sore throat and hoarseness

Skin

Diaphoresis
erythema 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, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Laboratory Test Findings

Clinically important changes in standard laboratory parameters were rarely associated with administration of RENITEC. 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 in which a causal relationship to therapy with RENITEC could not be excluded.

4.9 **Overdosage**

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, concomitant with blockade of the renin-angiotensin system, and stupor. 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. Enalaprilat may be removed from the general circulation by hemodialysis.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic Properties**

Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance angiotensin II.

Enalaprilat is a substance 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, which plays a major role in the regulation of blood pressure, 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. Abrupt withdrawal of RENITEC has not been associated with rapid increase in blood pressure.

The onset of action after intravenous administration of enalaprilat usually occurs within a few minutes of administration with the maximum effect occurring within 4 hours.

The duration of hemodynamic effects appears to be dose-related. However, for doses within the recommended dosage range, the duration of effect of RENITEC I.V. in most patients is approximately six hours.

Antihypertensive treatment with RENITEC leads to a significant regression of left ventricular hypertrophy with preservation of left ventricular systolic performance.

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.

Chronic administration of RENITEC to patients with essential hypertension and renal insufficiency may be associated with improvements in renal function, evidenced by increased glomerular filtration rate.

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.

Clinical data have shown that enalapril reduced the frequency of ventricular arrhythmias in patients with heart failure, although the underlying mechanisms and clinical significance are not known.

5.2 **Pharmacokinetic Properties**

There is no evidence for significant metabolism of enalaprilat.

Following intravenous administration of enalaprilat, mean urinary recovery of enalaprilat exceeded 90% of the administered dose. Serum profiles for enalaprilat at all tested doses were polyexponential with a prolonged terminal phase similar to that for enalaprilat following oral administration of enalapril maleate. This prolonged terminal phase is apparently associated with binding to ACE.

Enalaprilat binding to human plasma, determined either by equilibrium dialysis or ultrafiltration, shows 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. 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, nor with dialysis of the drug.

The effective half-life for accumulation of enalaprilat based on the oral administration of multiple doses of oral RENITEC is 11 hours. Studies in dogs indicated that enalaprilat does not cross the blood-brain barrier.

5.3 **Preclinical Data on Safety**

The safety of enalapril has been thoroughly investigated in mice, rats, dogs and monkeys to assess its general toxicity.

Acute toxicity: oral LD₅₀ 2000 mg/kg in mice and rats.

Subacute and chronic toxicity:

Rats: In rats treated with 10, 30 and 90 mg/kg/day of enalapril for up to one year, a slight decreased average body weight gains occurred at all dosage levels; serum urea nitrogen values were elevated in rats given 30 or 90 mg/kg/day, however no drug related histological changes were seen in the kidneys.

Dogs: Dogs treated with 15 mg/kg/day for up to one year showed no drug-induced changes.

Monkeys: Monkeys treated with up to 30 mg/kg/day of enalapril for one month showed no drug-related changes.

6. **PHARMACEUTICAL DATA**

6.1 **List of Excipients**

Each ampoule of 1 ml of RENITEC I.V. contains: benzylic alcohol, sodium chloride, sodium hydroxide and water for injection.

6.2 **Incompatibilities**

None described (see 4.2 Compatibility and Stability)

6.3 **Validity Period**

3 years

6.4 **Special Precautions for Preservation**

Store below 30⁰ (86⁰F) and avoid transient temperatures above 50⁰ (122⁰F).

6.5 **Nature and Contents of Recipient**

Glass ampoule type I, each containing 1 ml of RENITEC I.V.
Package with 5 ampoules. PVP _____(IVA)

6.6 **Instructions for Use/Handling**

Administer intravenously over at least 5 minutes and in certain cases over not less than 1 hour (see 4.2)

WITH MEDICAL PRESCRIPTION

ALL DRUGS SHOULD BE KEPT OUT OF CHILDREN'S REACH.

6.7 **Name and Address of the Titular Authorized to Commercialize**

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