PHYSICIANS CIRCULAR

Tablets

RENITEC®†

Oral Tablet (enalapril maleate, USP)

RENITEC (enalapril maleate, USP) is 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, non-sulphydryl angiotensin converting enzyme inhibitor.

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

RENITEC is also indicated in the treatment and prevention of heart failure.

A multicenter, placebo-controlled, double-blind study of left ventricular dysfunction (SOLVD) assessed the effects of RENITEC in 6,797 patients. 2,569 patients with all degrees of symptomatic heart failure (primarily mild to moderate New York Heart Association Class II and III) were randomized into the Treatment Arm, and 4,228 patients with asymptomatic left ventricular dysfunction were randomized into the Prevention Arm. The combined results demonstrated an overall reduced risk for the development of major ischemic events. RENITEC decreased the incidence of myocardial infarction and reduced the number of hospitalizations for unstable angina pectoris in patients with left ventricular dysfunction.

In addition, in the Prevention Arm, RENITEC significantly prevented the development of symptomatic heart failure and reduced the number of hospitalizations for heart failure. In the Treatment Arm, RENITEC, as an adjunct to conventional therapy, significantly reduced overall mortality and hospitalization for heart failure and improved NYHA functional class.

In a similar study involving 253 patients with severe heart failure (New York Heart Association Class IV), RENITEC was shown to improve symptoms and reduce mortality significantly.

The cardioprotective properties of RENITEC were demonstrated in these studies by the beneficial effects on survival and retardation of the progression of heart failure in patients with symptomatic heart failure; retardation of the development of symptomatic heart failure in asymptomatic patients with left ventricular dysfunction; and prevention of coronary ischemic events in patients with left ventricular dysfunction, specifically reduction in the incidence of myocardial infarction and reduction in hospitalization for unstable angina pectoris.

† Registered Trademark

INDICATIONS

Treatment of:

* **All Grades of Essential Hypertension**

* **Renovascular Hypertension**

* **All Degrees of Heart Failure**

In patients with symptomatic heart failure, RENITEC is also indicated to:

- Improve Survival
- Retard the Progression of Heart Failure
- Reduce Hospitalization for Heart Failure

* **Prevention of Symptomatic Heart Failure**

In asymptomatic patients with left ventricular dysfunction, RENITEC is indicated to:

- Retard the Development of Symptomatic Heart Failure
- Reduce Hospitalization for Heart Failure

* **Prevention of Coronary Ischemic Events** in Patients with Left Ventricular Dysfunction

RENITEC is indicated to:

- Reduce the Incidence of Myocardial Infarction
- Reduce Hospitalization for Unstable Angina Pectoris

DOSAGE AND ADMINISTRATION

Oral:

Since absorption of Tablets RENITEC is not affected by food, the tablets may be administered before, during, or after meals.

ESSENTIAL HYPERTENSION
The initial dose is 10 to 20 mg, depending on the degree of hypertension, and is given once daily. 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 one 20 mg tablet taken once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 40 mg daily.

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. If this is not possible, the initial dose of RENITEC should be low (5 mg or less) 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, the 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	<80 >30 mL/min.	5 - 10 mg
Moderate Impairment	≤30 >10 mL/min.	2.5 - 5 mg
Severe Impairment. Normally, these patients will be on dialysis.*	≤10 mL/min.	2.5 mg on dialysis days**

* See PRECAUTIONS - Hemodialysis Patients.

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

HEART FAILURE/ASYMPTOMATIC LEFT VENTRICULAR DYSFUNCTION

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. RENITEC may be used in the management of symptomatic heart failure usually with diuretics and, where appropriate, digitalis. 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 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. In patients with symptomatic heart failure, this dosage regimen was effective in reducing mortality.

Blood pressure and renal function should be monitored closely both before and after starting treatment with RENITEC (see PRECAUTIONS) 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 also should be monitored (see DRUG INTERACTIONS).

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 and in patients with hereditary or idiopathic angioedema.

PRECAUTIONS

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.

AORTIC STENOSIS/HYPERTROPHIC CARDIOMYOPATHY

As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.

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, usually 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. 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 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.

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.

HYPERKALEMIA - See also DRUG INTERACTIONS SERUM POTASSIUM

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, 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. Hyperkalemia can cause serious, sometimes fatal, arrhythmias.

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

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 DRUG INTERACTIONS.)

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.

In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated.

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.

PEDIATRIC USE

The safety and effectiveness of Tablets RENITEC have been established in hypertensive pediatric patients age 1 month to 16 years. Use of Tablets RENITEC in these age groups is supported by evidence

from adequate and well-controlled studies of Tablets RENITEC in pediatric and adult patients as well as by published literature in pediatric patients.

In a multiple dose pharmacokinetic study in 40 hypertensive pediatric patients, excluding neonates, Tablets RENITEC was generally well tolerated. Pharmacokinetics following oral administration of enalapril are similar in these patients and comparable to historical values in adults.

In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age, 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. In this study, Tablets RENITEC was generally well tolerated.

The adverse experience profile for pediatric patients is not different from that seen in adult patients.

Tablets 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.

DRUG INTERACTIONS

ANTIHYPERTENSIVE THERAPY

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

SERUM POTASSIUM – See also PRECAUTIONS, HYPERKALEMIA

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

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. In diabetic patients treated with oral

antidiabetic agents or insulin, glycemic control should be closely monitored for hypoglycemia, especially during the first month of treatment with an ACE inhibitor.

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.

NON-STEROIDAL ANTI-IMFLAMMATORY DRUGS including SELECTIVE CYCLOOXYGENASE-2 INHIBITORS

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, the coadministration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

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.

SIDE EFFECTS

RENITEC has been demonstrated to be generally well tolerated. In clinical studies, the overall incidence of side effects was no greater with RENITEC than with placebo. For the most part, side effects 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.

Hypersensitivity/Angioneurotic Edema

Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (see PRECAUTIONS). In very rare cases, intestinal angioedema has been reported with angiotensin converting enzyme inhibitors including enalapril.

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
Raynaud's phenomenon

ENDOCRINE
syndrome of inappropriate antidiuretic hormone secretion (SIADH)

GASTROINTESTINAL
ileus
pancreatitis
hepatic failure
hepatitis - either hepatocellular or cholestatic
jaundice
abdominal pain
vomiting
dyspepsia
constipation
anorexia
stomatitis

METABOLIC
Cases of hypoglycemia in diabetic patients on oral antidiabetic agents or insulin have been reported (see DRUG INTERACTIONS).

NERVOUS SYSTEM/ PSYCHIATRIC
depression
confusion
somnolence
insomnia
nervousness
paresthesia
vertigo
dream abnormality

RESPIRATORY
pulmonary infiltrates
bronchospasm/asthma
dyspnea
rhinorrhea
sore throat and hoarseness

SKIN
diaphoresis
erythema multiforme
exfoliative dermatitis
Stevens-Johnson syndrome
toxic epidermal necrolysis
pemphigus
pruritus
urticaria
alopecia

OTHER
impotence
flushing
taste alteration
tinnitus
glossitis
blurred vision

A 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.

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.

OVERDOSAGE

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Serum enalaprilat levels 100- 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 available, angiotensin II infusion may be beneficial. If ingestion is recent, induce emesis. Enalaprilat may be removed from the general circulation by hemodialysis. (See PRECAUTIONS, Hemodialysis Patients).

STORAGE

Store below 30°C (86°F) and avoid transient temperatures above 50°C (122°F).

AVAILABILITY

RENITEC® Tablets 5 mg, 10 mg and 20mg are supplied in blister packs of 20's (10's x 2 strips).