Enalapril Maleate / Hydrochlorothiazide

Core Safety Profile

4.3 Contra-indications

- Hypersensitivity to enalapril maleate, hydrochlorothiazide, or any of the excipients of <CO-RENITEC>.
- Severe renal impairment (creatinine clearance ≤30 ml/min).
- Anuria.
- History of angioneurotic edema associated with previous ACE-inhibitor therapy.
- Hereditary or idiopathic angioedema.
- Hypersensitivity to sulfonamide-derived drugs.
- Second and third trimesters of pregnancy (see section 4.4 and 4.6).
- Severe hepatic impairment.

4.4 Special warnings and precautions for use

Enalapril Maleate-Hydrochlorothiazide

Hypotension and Electrolyte Fluid Imbalance

Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving <CO-RENITEC>, symptomatic hypotension is more likely to occur if the patient has been volume - depleted, e.g., by diuretic therapy, dietary salt restriction, diarrhea or vomiting (see sections 4.5 and 4.8). Regular determination of serum electrolytes should be performed at appropriate intervals in such patients. Special attention should be paid 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. In hypertensive patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed.

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.

Renal Function Impairment

<CO-RENITEC> should not be administered to patients with renal insufficiency (creatinine clearance <80 ml/min. and >30 ml/min.) until titration of enalapril has shown the need for the dose present in this formulation (see section 4.2).

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 (see Special warnings and precautions for use, Enalapril Maleate, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4). If this occurs, therapy with <CO-RENITEC> should be discontinued. This situation should raise the possibility of underlying renal artery stenosis (see Special warnings and precautions for use, Enalapril Maleate, Renovascular Hypertension in section 4.4).

Hyperkalemia

The combination of enalapril and a low-dose diuretic cannot exclude the possibility of an hyperkalemia to occur (see Special warnings and precautions for use, Enalapril Maleate, Hyperkalemia in section 4.4).

Lithium

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

Lactose

<CO-RENITEC> contains less than 200 mg of lactose per tablet . Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Enalapril Maleate

Aortic Stenosis/Hypertrophic Cardiomyopathy

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

Renal Function Impairment

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 (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Hydrochlorothiazide, Renal Function Impairment in section 4.4).

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 and monitoring of renal function.

Kidney Transplantation

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

Hemodialysis Patients

The use of enalapril is not indicated in patients requiring dialysis for renal failure. 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.

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 (see Special warnings and precautions for use, Hydrochlorothiazide, Hepatic Disease in section 4.4).

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.

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 Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Hyperkalemia; Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 and section 4.5).

Diabetic Patients

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 Special warnings and precautions for use, Hydrochlorothiazide, Metabolic and Endocrine Effects in section 4.4 and section 4.5).

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 enalapril maleate. This may occur at any time during treatment. In such cases, <CO-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 Whites. However, in general it appears that Blacks have an increased risk for angioedema.

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 anaphylactic reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis.

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

Enalapril blocks angiotensin II formation and therefore impairs the ability of patients undergoing major surgery or anesthesia with agents that produce hypotension to compensate via the renin-angiotensin system. Hypotension which occurs due to this mechanism can be corrected by volume expansion (see section 4.5).

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.

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.

Hydrochlorothiazide

Renal function Impairment

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30 ml/min. or below (i.e., moderate or severe renal insufficiency) (see section 4.2 and Special warnings and precautions for use, Enalapril Maleate-Hydrochlorothiazide, Renal Function Impairment; Enalapril Maleate, Renal Function Impairment in section 4.4).

Hepatic Disease

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma (see Special warnings and precautions for use, Enalapril Maleate, Hepatic Failure in section 4.4).

Metabolic and Endocrine Effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents including insulin, may be required (see Special warnings and precautions for use, Enalapril Maleate, Diabetic Patients in section 4.4).

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy; however, at the 12.5 mg dose contained in <CO-RENITEC>, minimal or no effect was reported.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. However, enalapril may increase urinary uric acid and thus attenuate the hyperuricemic effect of hydrochlorothiazide.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides (including hydrochlorothiazide) can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia, and hypochloremic alkalosis). Warning signs of fluid or electrolyte imbalance are xerostomia, thirst, weakness, lethargy, somnolence, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Although hypokalemia may develop during use of thiazide diuretics, concurrent therapy with enalapril may reduce diuretic-induced hypokalemia. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5).

Hyponatremia may occur in edematous patients in hot weather. Chloride deficit is generally mild and does usually not require treatment.

Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of latent hyperparathyroidism. Thiazides should be discontinued before testing parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia.

Anti-doping test

Hydrochlorothiazide contained in this medicinal product can produce a positive analytic result in an anti-doping test.

Hypersensitivity

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

4.5 Interaction with other medicinal products and other forms of interaction

Enalapril Maleate-Hydrochlorothiazide

Other Antihypertensive Agents

Concomitant use of these agents may increase the hypotensive effects of enalapril and hydrochlorothiazide. 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 <CO-RENITEC> with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4.)

Non-Steroidal Anti-Inflammatory Drugs

Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor or may decrease the diuretic, natriuretic and antihypertensive effects of diuretics.

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).

Enalapril Maleate

Potassium-sparing Diuretics or Potassium Supplements

ACE inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium (see 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 sections 4.2 and 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic or by increasing volume or salt intake.

Tricyclic Antidepressants/Antipsychotics/Anesthetics

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).

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics

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

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.

Hydrochlorothiazide

Nondepolarizing Muscle Relaxants

Thiazides may increase the responsiveness to tubocurarine.

Alcohol, Barbiturates, or Opioid Analgesics
Potentiation of orthostatic hypotension may occur.

Antidiabetic Drugs (Oral Agents and Insulin)
Dosage adjustment of the antidiabetic drug may be required (see section 4.8).

Cholestyramine and Colestipol Resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Increasing the QT Interval (e.g., quinidine, procainamide, amiodarone, sotalol)
Increased risk of torsades de pointes.

Digitalis Glycosides
Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.

Kaliuretic Diuretics (e.g., Furosemide), Carbenoxolone, or Laxative Abuse
Hydrochlorothiazide may increase the loss of potassium and/or magnesium.

Pressor Amines (e.g., Noradrenaline)
The effect of pressor amines may be decreased.

Cytostatics (e.g., Cyclophosphamide, Methotrexate)
Thiazides may reduce the renal excretion of cytotoxic drugs and potentiate their myelosuppressive effects.

4.6 Pregnancy and lactation

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).

Prolonged exposure to hydrochlorothiazide during the third trimester of pregnancy may cause a feto-placental ischemia and growth retardation. Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term. Neonatal jaundice may also occur.

Hydrochlorothiazide can reduce plasma volume as well as uteroplacental blood flow.

<CO-RENITEC> is not recommended during lactation. Both enalapril and hydrochlorothiazide are excreted in human milk. Thiazides during breast-feeding have been associated with decrease or even suppression of milk lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalemia and nuclear icterus might occur. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of this therapy for the mother.

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. (See section 4.8)

4.8 Undesirable effects

Side effects reported with <CO-RENITEC>, enalapril alone or hydrochlorothiazide alone either during clinical studies or after the drug was marketed include:

[Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <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, leukopenia, pancytopenia, lymphadenopathy, autoimmune diseases

Endocrine disorders:

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

Metabolism and Nutrition Disorders:

common: hypokalemia, increase of cholesterol, increase of triglycerides, hyperuricemia

uncommon: hypoglycemia (see section 4.4), hypomagnesemia, gout

rare: increase in blood glucose

very rare: hypercalcemia

(see section 4.4)

Nervous System and Psychiatric Disorders:

common: headache, depression, syncope, taste alteration

uncommon: confusion, somnolence, insomnia, nervousness, paraesthesia, vertigo, decreased libido

rare: dream abnormality, sleep disorders, paresis (due to hypokalemia)

Eye Disorders:

very common: blurred vision

Ear and Labyrinth Disorders:

uncommon: tinnitus

Cardiac and Vascular Disorders:

very common: dizziness

common: hypotension, orthostatic hypotension, rhythm disturbances, angina pectoris, tachycardia

uncommon: flushing, 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, respiratory distress (including pneumonitis and pulmonary edema), rhinitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal Disorders:

very common: nausea

common: diarrhea, abdominal pain

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

rare: stomatitis/aphthous ulcerations, glossitis

very rare: intestinal angioedema

Hepatobiliary Disorders:

rare: hepatic failure, hepatic necrosis (may be fatal), hepatitis – either hepatocellular or cholestatic, jaundice, cholecystitis (in particular in patients with pre-existing cholelithiasis)

Skin and Subcutaneous Tissue Disorders:

common: rash (exanthema)

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, purpura, cutaneous lupus erythematosus, erythroderma, pemphigus

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.

Musculoskeletal, Connective Tissue and Bone Disorders:

common: muscle cramps

uncommon: arthralgia

Renal and Urinary Disorders:

uncommon: renal dysfunction, renal failure, proteinuria

rare: oliguria, interstitial nephritis

Reproductive System and Breast Disorders:

uncommon: impotence

rare: gynecomastia

General Disorders and Administration Site Conditions:

very common: asthenia

common: chest pain, fatigue

uncommon: malaise, fever

Investigations:

common: hyperkalemia, increases in serum creatinine

uncommon: increases in blood urea, hyponatremia

rare: elevations of liver enzymes, elevations of serum bilirubin

4.9 Overdose

No specific information is available on the treatment of overdosage with <CO-RENITEC>. Treatment is symptomatic and supportive. Therapy with <CO-RENITEC> should be discontinued and the patient observed closely. Suggested measures include induction of emesis, administration of activated charcoal, and administration of a laxative if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalapril Maleate

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 maleate, 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.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.