Anuria.
• VHypersensitivity to other sulfonamide-derived drugs.
• Stenosis of the renal arteries.

4.4 Special warnings and special precautions for use

Symptomatic Hypotension
Symptomatic hypotension may occur occasionally following the initial dose of ‘Co-Renitec’. In hypertensive patients, hypotension is more likely to occur if the patient has been volume-depleted, e.g. by prior of simultaneous use of diuretics, dietary salt restriction, dialysis, diarrhea or vomiting, or in the event of serious renin-dependent hypotension. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Particular consideration should be given when therapy is administered to patients with ischemic heart or cerebrovascular disease because 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, but care should be observed. Treatment with ‘Co-Renitec’ can be initiated only when blood volume and blood pressure have been effectively restored, in which case reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

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
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). ‘Co-Renitec’ should not be administered to patients with renal insufficiency (creatinine clearance < 80 ml/min) until titration of the individual components has shown the need for the doses present in the combination tablet. In these cases ‘Co-Renitec’ should not be used as initial therapy since the recommended initial dosage of enalapril amounts to 5 mg or less in these patients. During the use of ‘Co-Renitec’ in patients with renal insufficiency it is desirable to monitor renal function.

Some hypertensive patients with no apparent pre-existing renal disease have developed usually minor and transient increases in blood urea and serum creatinine when enalapril has been given concomitantly with a diuretic. If this occurs during therapy with ‘Co-Renitec’, the combination should be discontinued. Reinstigation of therapy at reduced dosage may be possible, or either of the components may be used appropriately alone.

Renovascular Hypertension
In some hypertensive patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen with angiotensin-converting enzyme (ACE) inhibitors. Co-Renitec should not be administered to patients with renovascular hypertension until titration of the individual components has shown the need for the doses present in the combination tablet. In these cases Co-Renitec should not be used as initial therapy since the recommended initial dosage of enalapril amounts to 5 mg or less in these patients. During the use of ‘Co-Renitec’ it is desirable to monitor renal function.

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.

Congestive Heart Failure
‘Co-Renitec’ should not be used as initial therapy in patients with hypertension and concomitant congestive heart failure in connection with the lower initial dosage of enalapril. Also one should be alert to deterioration of renal function. In patients with heart failure, there is also an increased risk of symptomatic hypotension, in particular in case of severe degrees, as may be reflected by concurrent use of high doses of diuretics, hyponatremia and functional renal impairment. Treatment of such patients should be initiated under medical supervision, and the patients should be followed closely whenever the dose of ‘Co-Renitec’ is adjusted.

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block 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.

Metabolic and Endocrine Effects of Hydrochlorothiazide
Thiazide therapy may impair glucose tolerance. Dosage adjustment or antidiabetic agents including insulin, may be required.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients.

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 enalapril. This may occur at any time during treatment. In such cases, enalapril
maleate 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 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 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).

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.

Anaphylactoid reactions during hymenoptera desensitization

Patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoiped by temporarily withholding ACE inhibitor therapy prior to each desensitization.

Anaphylactoid Reactions during LDL Apheresis

Patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions are avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Hemodialysis Patients

The use of ‘Co-Renitec’ is not indicated in patients requiring dialysis for renal failure (see Posology and method of administration). Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Therefore it is recommended to not use such membranes in these patients.

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.

Use in the Elderly

In the elderly ‘Co-Renitec’ should be used with caution. Allowance should be made for pre-existing renal insufficiency.

Pediatric use

Safety and effectiveness in children have not been established.

4.5 Interactions with other medicinal products and other forms of interaction

Additive effects may occur when enalapril is used together with other antihypertensive therapy. The combination of enalapril with betablockers, methyldopa, or calcium entry blockers has been shown to improve the efficacy of lowering the blood pressure. Propranolol coadministered with enalapril 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 or adrenergic blocking agents, combined with enalapril, should only be administered under careful observation of the patient.

When administered concurrently the following drugs may interact with thiazide diuretics.

Alcohol, Barbiturates, or Narcotic Analgesics - potentionation of orthostatic hypotension may occur.

Antidiabetic Drugs (oral agents and insulin) - dosage adjustment of the antidiabetic drug may be required.

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. Corticosteroids, ACTH - intensified electrolyte depletion particularly hypokalemia. Pressor Amines (e.g., Epinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use. Prostaglandin Synthetase Inhibitors - in some patients, the administration of a prostaglandin synthetase inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics. Serum Potassium - The potassium-losing effect of thiazide diuretics is usually attenuated by the effect of enalapril. Serum potassium usually remains within normal limits. The use of potassium supplements, potassium-sparing agents, or potassium containing salt substitutes particularly in patients with impaired renal function, may lead to a significant increase in serum potassium. Lithium - Diuretics or ACE inhibitors reduce the renal clearance and add a high risk of lithium toxicity, concomitant use is not recommended. Circulars for lithium preparations should be consulted before use of such preparations with ‘Co-Renitec’. Non-Steroidal Anti-Inflammatory Drugs The administration of a non-steroidal anti-inflammatory drug may reduce the antihypersensitive effect of an ACE inhibitor. Especially in some patients with compromised renal function or patients who are volume-depleted who are being treated with non-steroidal anti-inflammatory drugs, the coadministration of ACE inhibitors may result in a further deterioration of renal function. These effects are usually reversible. Non-Depolarizing Muscle Relaxants - Thiazides may increase the responsiveness to tubocurarine.

4.6 Pregnancy and lactation
If children are desired and in case of pregnancy, ‘Co-Renitec’ should be discontinued, unless it is considered life-saving for the mother. Furthermore patient should contact the treating physician in order to decide on alternative treatment. 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 disorders, including hypotension, renal insufficiency, hyperkalemia and/or skull hypoplasia. As a result of reduced renal function, oligohydramnios may occur in the fetus. This may lead to limb contractures, craniofacial deformations and hypo-plastic lung development. In addition, prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported; it is not clear, however, whether these occurrences were due to ACE inhibitor exposure. If ‘Co-Renitec’ is used, the patient should be apprised of the potential hazard to the fetus. There is insufficient experience with the safety of the use of ‘Co-Renitec’ during embryonic development (first two months of pregnancy); so far, negative fetal effects do not appear to be the result of exposure in early pregnancy. Experiments in animals have demonstrated that ACE inhibitors adversely affect late-fetal development, resulting in fetal mortality and congenital defects of especially the cranium. The latter defect would be a result of the pharmacologic action of the agent and be associated with the oligohydramnios caused. In those rare cases where ACE inhibitor use during pregnancy is deemed essential, serial ultrasound examinations should be performed to assess growth retardation and the intraamniotic environment. If oligohydramnios is detected, ‘Co-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. Neonates whose mothers have taken ‘Co-Renitec’ should be closely observed for hypotension, oliguria and hyperkalemia. Enalapril, which crosses the placen-
A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis and arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Hypersensitivity/Angioneurotic Edema: angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely (see Special warnings and special precautions for use).

In very rare cases, intestinal angiodema has been reported with angiotensin converting enzyme inhibitors including enalapril.

Laboratory Test Findings: Hyperglycemia, hyperuricemia and hypokalemia have been reported. Increases in blood urea nitrogen and serum creatinine and elevations of liver enzymes and/or serum bilirubin have been seen. These are usually reversible upon discontinuation of ‘Co-Renitec’. Hyperkalemia has occurred.

Decreases in hemoglobin, hematocrit have been reported. Decreases in platelets and white cell count, and rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported, but a causal relationship to ‘Co-Renitec’ has not been established.

Additional side-effects that have been seen with one of the individual components and may be potential side-effects with ‘Co-Renitec’ are following:

**Enalapril:** ileus, hepatic failure, hepatitis either hepatocellular or cholestatic, jaundice, depression, confusion, dream abnormality, pulmonary infiltrates, bronchospasm /asthma, sore throat and hoarseness, rhythm disturbances, angina pectoris, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients, Raynaud’s phenomenon, rhinorrhea, photosensitivity, alopecia, flushing, taste alteration, anorexia, blurred vision, urticaria, stomatitis, glossitis, oliguria, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, pemphigus. Hyponatremia has occurred.

**Hydrochlorothiazide:** anorexia, gastric irritation,
jaundice, (intrahepatic cholestatic jaundice), sialoadenitis, xanthophsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia, purpura, photosensitivity, fever, urticaria, necrotizing angitis (vasculitis), respiratory distress (including pneumonia and pulmonary edema), interstitial nephritis, anaphylactic reaction, toxic epidermal necrolysis, glycosuria, electrolyte imbalance, including hyponatremia, restlessness, muscle spasm, transient blurred vision.

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 active charcoal, administration of a laxative and/or gastric lavage if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

Enalapril: The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. If available, angiotensin II infusion may be beneficial. Enalaprilat may be removed from the general circulation by hemodialysis (See Precautions, Hemodialysis patients).

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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
‘Co-Renitec’ is a combination of an angiotensin converting enzyme inhibitor (enalapril) and a diuretic (hydrochlorothiazide).

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 removal 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, which plays a major role in the regulation of blood pressure, enalapril may have a blood pressure lowering effect even in patients with low-renin hypertension.

Hydrochlorothiazide is a diuretic and antihypertensive agent which increases plasma renin activity. The antihypertensive effects of the two components are additive and are usually sustained for 24 hours. A higher percentage of patients with hypertension respond satisfactorily to ‘Co-Renitec’ than to either component administered alone. The enalapril component of ‘Co-Renitec’ usually attenuates the potassium-loss associated with hydrochlorothiazide.

5.2 Pharmacokinetic properties

Enalapril
Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril is approximately 60-70%.

Following absorption, oral enalapril is rapidly and extensively hydrolyzed to enalaprilat, a potent angiotensin-converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur three to four hours after an oral dose of enalapril. 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 to ACE. In subjects with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enalapril. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. The absorption of oral 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.

**Hydrochlorothiazide**
When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

**Enalapril-hydrochlorothiazide**
Concomitant multiple doses of enalapril and hydrochlorothiazide have little or no effect on the bioavailability of these drugs. The combination tablet is bioequivalent to concomitant administration of the separate entities.

**5.3 Preclinical safety data**
In animal studies, ACE inhibitors adversely affected late-fetal development (see Pregnancy and lactation). No further particular data.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**
Sodium hydrogen carbonate, lactose, maize starch, iron oxide yellow (E172), pregelatinized starch, magnesium stearate (E572).

**6.2 Incompatibilities**
No particulars.

**6.3 Shelf-life**
The shelf-life is three years when stored at 15-30°C in the original package.

**6.4 Special precautions for storage**
Do not store above 25°C; store in the original package.

**6.5 Nature and contents of container**
Box with three blisters of 10 tablets each.

**6.6 Instructions for use and handling**
No particulars.

**7. MARKETING AUTHORIZATION HOLDER**
MERCK SHARP & DOHME B.V.
P.O. Box 581, 2003 PC HAARLEM

**8. MARKETING AUTHORIZATION NUMBER**
Entered in the register under RVG 11825

**9. DATE OF APPROVAL/REVISION OF THE SPC**
17 August 1988

**10. DATE OF REVISION OF THE TEXT**
21 January 2004
Here above is the latest Summary of Products Characteristics submitted to the Ministry of Health Lebanon Nov 05, Kuwait Nov 05, Oman Nov 05