PHYSICIANS CIRCULAR

Tablets

CO-RENITEC®

(enalapril maleate and hydrochlorothiazide, USP)

CO-RENITEC* (enalapril maleate and hydrochlorothiazide, USP) is a combination of an angiotensin converting enzyme inhibitor (enalapril maleate) and a diuretic (hydrochlorothiazide).

CO-RENITEC is highly effective in the treatment of hypertension. The antihypertensive effects of the two components are additive and are sustained for at least 24 hours. A higher percentage of patients with hypertension respond satisfactorily to CO-RENITEC than to either component administered alone.

INDICATIONS

CO-RENITEC is indicated for the treatment of hypertension in patients for whom combination therapy is appropriate.

DOSAGE AND ADMINISTRATION

CO-RENITEC is supplied as tablets for oral administration.

CO-RENITEC 10/25 contains enalapril maleate 10 mg and hydrochlorothiazide 25 mg.

HYPERTENSION

The usual dosage is one or two tablets, administered once daily. The dosage should be adjusted according to blood pressure response.

PRIOR DIURETIC THERAPY

Symptomatic hypotension may occur following the initial dose of CO-RENITEC; this is more likely in patients who are volume- or salt-depleted as a result of prior diuretic therapy. The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with CO-RENITEC.

DOSAGE IN RENAL INSUFFICIENCY

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).

In patients with creatinine clearance of >30 and <80 mL/min., CO-RENITEC should be used only after titration of the individual components.

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The recommended initial dose of enalapril maleate, when used alone, in mild renal insufficiency is 5 to 10 mg.

CONTRAINDICATIONS

Anuria.

CO-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.

Hypersensitivity to other sulfonamide-derived drugs.

PRECAUTIONS

HYPOTENSION AND ELECTROLYTE/FLUID IMBALANCE

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during intercurrent diarrhea or vomiting. 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. Following restoration of effective blood volume and pressure 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.

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. Reinstitution of therapy at reduced dosage may be possible; or either of the components may be used appropriately alone.

In some 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.

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.

SURGERY/ANESTHESIA

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalaprilat 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.

METABOLIC AND ENDOCRINE EFFECTS

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents including insulin, may be required.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium. Marked hypercalcinemia 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; 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.

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 maleate. 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. 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).

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

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

The use of CO-RENITEC is not indicated in patients requiring dialysis for renal failure (see DOSAGE AND ADMINISTRATION). 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.

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

USE IN PREGNANCY

The use of CO-RENITEC during pregnancy is not recommended. When pregnancy is detected, CO-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.

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

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

If CO-RENITEC is used during pregnancy, the patient should be apprised of the potential hazard to the fetus. In those rare cases where use during pregnancy is deemed essential, serial ultrasound examinations should be performed to assess 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.

Infants whose mothers have taken CO-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.

There is no experience with the removal of hydrochlorothiazide, which also crosses the placenta, from the neonatal circulation.

NURSING MOTHERS

Both enalapril and thiazides appear in human milk. If use of the drug is deemed essential, the patient should stop nursing.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

USE IN THE ELDERLY

In clinical studies the efficacy and tolerability of enalapril maleate and hydrochlorothiazide, administered concomitantly, were similar in both elderly and younger hypertensive patients.

DRUG INTERACTIONS

Additive effects may occur when enalapril maleate is used together with other antihypertensive therapy.

OTHER ANTIHYPERTENSIVE THERAPY

The combination of enalapril maleate with beta-adrenergic blocking agents, methyldopa, or calcium entryblockers has been shown to improve the efficacy of lowering the blood pressure.

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 NARCOTICS

Potentiation 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., ADRENALIN)

Possible decreased response to pressor amines but not sufficient to preclude their use.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

SERUM POTASSIUM – See also PRECAUTIONS, HYPERKALEMIA

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

LITHIUM

Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity: concomitant use is not recommended. Refer to the package inserts for lithium preparations before use of such preparations.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS 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.

NON-DEPOLARIZING MUSCLE RELAXANTS

Thiazides may increase the responsiveness to tubocurarine.
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

CO-RENITEC is usually well-tolerated. In clinical studies, side effects have usually been mild and transient, and in most instances have not required interruption of therapy.

The most common clinical side effects were dizziness and fatigue, which generally responded to dosage reduction and seldom required discontinuation of therapy.
Other side effects (1 - 2%) were: muscle cramps, nausea, asthenia, orthostatic effects including hypotension, headaches, cough, and impotence.

Less common side effects which occurred either during controlled trials or during marketed use include:

CARDIOVASCULAR
syncope
non-orthostatic hypotension
palpitation
tachycardia
chest pain

ENDOCRINE
syndrome of inappropriate antidiuretic hormone secretion (SIADH)

GASTROINTESTINAL
pancreatitis
diarrhea
vomiting
dyspepsia
abdominal pain
flatulence
constipation

NERVOUS SYSTEM/PSYCHIATRIC
insomnia
somnolence
paresthesia
vertigo
nervousness

RESPIRATORY
dyspnea

SKIN
Stevens-Johnson syndrome
rash
pruritus
diaphoresis

OTHER
renal dysfunction
renal failure
decreased libido
dry mouth
gout
tinnitus
arthralgia

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.

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.

LABORATORY TEST FINDINGS

Clinically important changes in standard laboratory parameters were rarely associated with administration of CO-RENITEC. Occasional hyperglycemia, hyperuricemia and hypokalemia have been noted. 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 CO-RENITEC. Hyperkalemia has occurred.

Decreases in hemoglobin and hematocrit have been reported.

POTENTIAL SIDE EFFECTS

Additional side effects that have been seen with one of the individual components and may be potential side effects with CO-RENITEC are the 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, Raynaud's phenomenon, possibly secondary to excessive hypotension in high risk patients, rhinorrhea, photosensitivity, alopecia, flushing, taste alteration, anorexia, blurred vision, urticaria, stomatitis, glossitis, oliguria, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitiS, pemphigus.

LABORATORY TEST FINDINGS

Hyponatremia has occurred.

HYDROCHLOROTHIAZIDE

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

OVERDOSAGE

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 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. 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 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.

AVAILABILITY

CO–RENITEC® Tablets are supplied in blister package of 20 tablets (10's x 2 strips). Each tablet contains 10 mg Enalapril Maleate, U.S.P. and 25 mg Hydrochlorothiazide, U.S.P.