CO-RENITEC®

COMPOSITION

Each tablet contains enalapril maleate 20 mg and hydrochlorothiazide 12.5 mg.

PHARMACEUTICAL FORM

Tablets.

CLINICAL PARTICULARS

Indications

Treatment of hypertensive patients who have insufficiently responded to treatment with enalapril or a diuretic as single therapy.

Dosage and method of administration

If patients are started on CO-RENITEC after the use of a diuretic as previous sole therapy, the diuretic therapy should be stopped for 2-3 days before CO-RENITEC is started. These patients should be closely observed for signs or symptoms of hypotension after the initial dose of CO-RENITEC (see Warnings and precautions).

The initial dosage is one half tablet, administered once daily. If necessary the dose may be increased to one tablet, administered once daily. The maximum dosage is two tablets, administered once daily. CO-RENITEC should not be given as initial dosage to patients with renal insufficiency and renovascular hypotension (see Warnings and precautions).

Contra-indications

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. Anuria. Hypersensitivity to other sulfonamidederived drugs. See also Use in pregnancy and during lactation.

WARNINGS AND PRECAUTIONS

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 presssure 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.

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 preexisting 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.

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 preferably be initiated in a hospital.

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 choiesterol 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. 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 such as subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) should be administered promptly.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (Also see Contraindications).

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.

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.

Pediatric use

Safety and effectiveness in children have not been established.

Use in the elderly

In the elderly CO-RENITEC should be used with caution. Allowance should be made for pre-existing renal insufficiency.

INTERACTIONS

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

The combination of enalapril with beta-adrenergic blocking agents, 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 - potentiation of orthostatic hypotension may occur.

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

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 - Lithium generally should not be given with diuretics or ACE inhibitors because they reduce its renal clearance and add a high risk of lithium toxicity. Circulars for lithium preparations should be, consulted before use of such preparations with CO-RENITEC.

Non-depolarizing muscle relaxants - Thiazides may increase the responsiveness to tubocurarine.

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PREGNANCY AND LACTATION

From clinical observations it has appeared that thiazides and ACE inhibitors may be harmful to the fetus: data are available that indicate that ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women; therefore, the use of enalapril during pregnancy is not recommended unless needed in a situation where other drugs cannot be used or are ineffective. If enalapril is used, the patient should be apprised of the potential hazard to the fetus.

Both enalapril and enalaprilate cross the human placenta. Infants whose mothers have taken enalapril should be closely observed. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome. However, there have been reports of hypotension, renal failure, hyperkalemia, and/or skull hypoplasia in the newborn when ACE inhibitors were used during the second and third trimesters of pregnancy. Maternal oligohydramnios, presumably representing decreased renal function in the fetus, has occurred and may result in limb contractures and craniofacial deformations. If oligohydramnios is observed, enalapril should be discontinued unless it is considered life-saving to the mother.

Thiazides cross the placental barrier and appear in cord blood. The possible hazards to the fetus include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occured in the adult.

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

ABILITY TO DRIVE AND USE MACHINES

No specific data are available. Some of the effects mentioned under side-effects may affect the ability to drive and/or to operate machinery.

UNDESIRABLE EFFECTS

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 which occurred either during controlled trials or during marketing use include:

Cardiovascular: syncope, non-orthostatic hypotension, palpitation, tachycardia, chest pain.

Gastrointestinal: 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 fever, serositis, vasculitis, myalgia 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 Warnings and precautions).

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, pancreatitis, hepatitis, either hepatocellular or cholestatic, jaundice, depression, confusion, bronchospasm/asthma, sore throat and hoarseness, rhythm disturbances, angina pectoris, myocardial infarction or cerebrovascular accident, 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.

Hyponatremia has occured.

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

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 and/or gastric lavage, 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. Enalaprilat may be removed from the general circulation by hemodialysis.

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.

PHARMACOLOGICAL PROPERTIES

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.

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 angiotension-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 subjets with normal renal function, steady state serum concentrations of enalaprilat were achieved by the fourth day of administration of enaiapril. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. The obsorption 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

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. 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. 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium hydrogen carbonate, lactose, maize starch, iron oxide yellow (E172), pregelatinized starch, magnesium stearate.

Incompatibilities

N.a.

Shelf life

The expiry date is mentioned on the package (mm/yy).

Special precautions for storage

Store at room temperature in the original package.

Nature and contents of the container

Blisters of 30 tablets.

MSD