PHYSICIANS CIRCULAR

Tablets

Co-Novatec
(lisinopril and hydrochlorothiazide, USP)

CO-NOVATEC (lisinopril and hydrochlorothiazide, USP) is a combination of an angiotensin converting enzyme inhibitor (lisinopril) and a diuretic (hydrochlorothiazide).

CO-NOVATEC is highly effective in the treatment of hypertension and the antihypertensive effect is usually sustained for 24 hours. A higher percentage of patients with hypertension respond satisfactorily to CO-NOVATEC than to either component administered alone.

INDICATIONS

Essential hypertension, for patients in whom combination therapy is appropriate.

DOSAGE AND ADMINISTRATION

CO-NOVATEC is supplied as tablets for oral administration.

CO-NOVATEC 20/12.5 mg contains lisinopril 20 mg and hydrochlorothiazide 12.5 mg.

ESSENTIAL HYPERTENSION

The usual dosage is one tablet, administered once daily. If necessary the dosage may be increased to two tablets, administered once daily.

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).

CO-NOVATEC is not to be used as initial therapy in any patient with renal insufficiency.

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

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

PRIOR DIURETIC THERAPY

Symptomatic hypotension may occur following the initial dose of CO-NOVATEC; this is more likely in patients who are volume and/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-NOVATEC. If this is not possible, treatment should be started with lisinopril alone, in a 5 mg dose.

CONTRAINDICATIONS

Anuria.

CO-NOVATEC 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. This was rarely seen in uncomplicated hypertensive patients but is more likely in the presence of fluid or electrolyte imbalance, e.g. volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur from prior diuretic therapy, dietary salt restriction, dialysis, or 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-NOVATEC should not be administered to patients with renal insufficiency (creatinine clearance $\leq$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 lisinopril has been given concomitantly with a diuretic. If this occurs during therapy with CO-NOVATEC, 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, lisinopril 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

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

Thiazides may decrease urinary calcium excretion and 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. However, lisinopril may increase urinary uric acid and thus may 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 lisinopril. This may occur at any time during treatment. In such cases, lisinopril 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-NOVATEC 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 non-productive, 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-NOVATEC 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-NOVATEC during pregnancy is not recommended. When pregnancy is detected, CO-NOVATEC 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-NOVATEC 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-NOVATEC 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-NOVATEC should be closely observed for hypotension, oliguria and hyperkalemia. Lisinopril, 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

It is not known whether lisinopril is secreted in human milk; however, thiazides do appear in human milk. Because of the potential for serious reactions from hydrochlorothiazide in nursing infants, a decision should be made whether to discontinue nursing or to discontinue CO-NOVATEC, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in children have not been established.

USE IN THE ELDERLY

Lisinopril, within a daily dosage range of 20 to 80 mg, was equally effective in elderly (65 years or older) and non-elderly hypertensive patients. In elderly hypertensive patients, monotherapy with lisinopril was as effective in reducing diastolic blood pressure as monotherapy with either hydrochlorothiazide or atenolol. In clinical studies, age did not affect the tolerability of lisinopril.

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

DRUG INTERACTIONS

SERUM POTASSIUM – See also PRECAUTIONS, HYPERKALEMIA

The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. 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-NOVATEC 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 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 co-administration 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.

DUAL BLOCKADE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, dual blockade of the renin-angiotensin-aldosterone system is associated with a higher frequency of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g., by adding an ACE inhibitor to an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function.

OTHER AGENTS

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 lisinopril.

SIDE EFFECTS

CO-NOVATEC 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 side effects that have been observed have been limited to those reported previously with lisinopril or hydrochlorothiazide.

The most common clinical side effect was dizziness, which generally responded to dosage reduction and seldom required discontinuation of therapy.

Other, less frequent, side effects were headache, dry cough, fatigue, hypotension including orthostatic hypotension.

Still less common were diarrhea, nausea, vomiting, pancreatitis, dry mouth, rash, gout, palpitation, chest discomfort, muscle cramps and weakness, syndrome of inappropriate antidiuretic hormone secretion (SIADH), paresthesia, asthenia and impotence.

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 lisinopril.

A symptom complex has been reported which may include some or all of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity, or other dermatologic manifestations may occur.

LABORATORY TEST FINDINGS

Laboratory side effects have rarely been of clinical importance. Occasional hyperglycemia, hyperuricemia and hyperkalemia or hypokalemia have been noted. Usually minor and transient increases in blood urea nitrogen and serum creatinine have been seen in patients without evidence of pre-existing renal impairment. If such increases persist, they are usually reversible upon discontinuation of CO-NOVATEC. Small decreases in hemoglobin and hematocrit have been reported frequently in hypertensive patients treated with CO-NOVATEC but were rarely of clinical importance unless another cause of anemia co-existed. Rarely, elevations of liver enzymes and/or serum bilirubin have occurred, but a causal relationship to CO-NOVATEC has not been established.

Other Side Effects
Other side effects reported with the individual components alone are listed below.

HYDROCHLOROTHIAZIDE

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

LISINOPRIL

myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS), tachycardia, abdominal pain, hepatitis - either hepatocellular or cholestatic, jaundice, mood alterations, mental confusion, bronchospasm, urticaria, pruritus, diaphoresis, alopecia, uremia, oliguria/anuria, renal dysfunction, acute renal failure, bone marrow depression manifest as anemia and/or thrombocytopenia and/or leukopenia, cutaneous pseudolymphoma.

OVERDOSAGE

No specific information is available on the treatment of overdosage with CO-NOVATEC. Treatment is symptomatic and supportive. Therapy with CO-NOVATEC should be discontinued and the patient observed closely. Suggested measures include induction of emesis and/or gastric lavage, if ingestion is recent, and correction of dehydration, electrolyte imbalance and hypotension by established procedures.

LISINOPRIL

The most likely feature of overdosage is hypotension, for which the usual treatment is intravenous infusion of normal saline solution, if available, angiotensin II may be beneficial.

Lisinopril 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-NOVATEC 20/12.5 mg Tablets are supplied in blister packs of 30's each (10's x 3 strips).