CO-TRUPRIL™

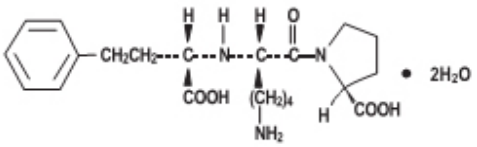
کو۔ٹروپرل

(LISINOPRIL + HYDROCHLOROTHIAZIDE)

Tablets 20mg+12.5mg

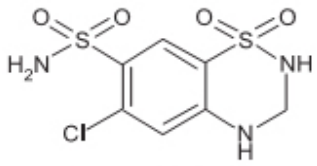
DESCRIPTION

CO-TRUPRIL (Lisinopril +Hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide. Lisinopril, a synthetic peptide derivative, is an oral long-acting angiotensin converting enzyme inhibitor. Chemically it is described as (S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate. Its molecular formula is $C_{21}H_{31}N_3O_5.2H_2O$ and its structural formula is:



Lisinopril dihydrate

Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its molecular formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide

QUALITATIVE & QUANTITATIVE COMPOSITION

CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) is available for oral administration as:

CO-TRUPRIL Tablets
Each tablet contains:
Lisinopril dihydrate equivalent to
Lisinopril USP....20mg
Hydrochlorothiazide USP...12.5mg

CLINICAL PHARMACOLOGY

Lisinopril and Hydrochlorothiazide

As a result of its diuretic effects, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, and decreases serum potassium. Administration of lisinopril blocks the renin-angiotensin aldosterone axis and tends to reverse the potassium loss associated with the diuretic.

Concomitant administration of lisinopril and hydrochlorothiazide has little or no effect on the bioavailability of either drug. The combination tablet is bioequivalent to concomitant administration of the separate entities.

Mechanism of Action:

Lisinopril

The mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system. Lisinopril is antihypertensive even in patients with low-renin hypertension.

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. Hydrochlorothiazide is a diuretic and antihypertensive. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacokinetics

Lisinopril

Lisinopril is slowly and incompletely absorbed following oral administration. About 25% of a given dose is absorbed on average, but the absorption varies considerably between individuals, ranging from about 6 to 60%. Peak concentrations in plasma are reported to occur after about 7 hours. Lisinopril is reported not to be significantly bound to plasma proteins. It is excreted unchanged in the urine. The effective half-life for accumulation following multiple doses is 12 hours in patients with normal renal function.

Hydrochlorothiazide

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life between 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

THERAPEUTIC INDICATIONS

CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) is indicated in the management of mild to moderate hypertension in patients who are not adequately controlled on monotherapy.

DOSAGE & ADMINISTRATION

The usual dosage of CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) is 1 tablet, administered once daily. CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) should be taken approximately the same time each day. If the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks at this dose level, the dose can be increased to 2 tablets administered once daily.

Renal Insufficient Patients

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

Prior Diuretic Therapy

The diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with CO-TRUPRIL (Lisinopril+Hydrochlorothiazide). If this is not possible, treatment should be started with lisinopril alone in a 2.5mg dose.

ADVERSE REACTIONS

CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) is usually well tolerated. Side effects have usually been mild and transient and in most cases have not required interruption of therapy.

General:

Common: Dizziness, headache, dry cough, fatigue, hypotension including orthostatic hypotension. Small decreases in hemoglobin and hematocrit.

Less Common: Diarrhea, nausea, vomiting, dry mouth, rash, gout, palpitations, chest discomfort, muscle cramps and weakness, paraesthesia, asthenia and impotence. Hyperglycemia, hyperuricemia and hyper or hypokalemia.

Rare: Pancreatitis, agranulocytosis, elevations of liver enzymes and/or serum bilirubin.

Laboratory Test Findings

Usually minor and transient increases in blood urea nitrogen and serum creatinine have been seen in patients without evidence of pre-existing renal impairment. Bone marrow depression, manifest as anemia and/or thrombocytopenia and/or leucopenia has been reported.

Hypersensitivity+Angioneurotic Edema

Angioneurotic edema of the face, extremities, lips, tongue glottis and/or larynx has been reported rarely. In very rare cases, intestinal angioedema has been reported.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations.

There may be other potential side effects that could be due to the individual

components alone.

CONTRAINDICATIONS

1. CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) 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.
2. CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) is contraindicated in patients who are hypersensitive to other sulphonamide-derived drugs.
3. CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) is contraindicated in patients with anuria.
4. CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) is contraindicated in pregnancy and treatment should be stopped if pregnancy is suspected.

PRECAUTIONS

Hypotension and Electrolyte/Fluid Imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision.

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.

Renal Function Impairment

Thiazides may not be appropriate diuretics for use in patients with renal impairment and are ineffective at creatinine clearance values of 30mL/min or below (i.e., moderate or severe renal insufficiency). Treatment should be started under close medical supervision with low doses and careful dose titration. Renal function should be monitored during the first few weeks of CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) therapy.

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.

Metabolic and Endocrine Effects

- Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. 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.

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 in breast-fed infants, a decision should be made whether to discontinue breast feeding or to discontinue CO-TRUPRIL (Lisinopril+Hydrochlorothiazide), taking into account the importance of the drug to the mother.

Drug Interactions

Agents Increasing Serum Potassium:

The potassium losing effect of thiazide diuretics is usually attenuated by the potassium conserving effect of lisinopril. Potassium sparing diuretics should be given only for documented hypokalemia with caution and with frequent monitoring of serum potassium since they may lead to a significant increase in serum potassium. Salt substitutes which contain potassium should also be used with caution.

Agents Affecting Sympathetic Activity:

Agents affecting sympathetic activity may be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to lisinopril.

Indomethacin:

Indomethacin may diminish the antihypertensive efficacy of concomitantly administered lisinopril.

Lithium:

Lithium generally should not be given with diuretics or ACE inhibitors. Diuretic agents and ACE inhibitors reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Corticosteroids (ACTH):

Intensified electrolyte depletion, particularly hypokalemia may occur when given concomitantly with thiazide diuretics.

Nonsteroidal Anti-inflammatory Drugs:

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs (NSAIDs), the co-administration of lisinopril may result in a further deterioration of renal function.

Tubocurarine:

Thiazides may increase the responsiveness to tubocurarine.

Insulin:

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

Alcohol, Barbiturates or Narcotics:

In the presence of thiazide diuretics, potentiation of orthostatic hypotension may occur.

Pressor Amines:

In the presence of thiazide diuretic, possible decreased response to pressor amines but not sufficient to preclude their use.

STORAGE

Store below 30°C.

Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

CO-TRUPRIL (Lisinopril+Hydrochlorothiazide) Tablets 20mg+12.5mg are available in blister pack of 28's.

Keep out of reach of children.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz Pharma (Pvt.) Limited, 29-30/27,
K.I.A., Karachi - 74900, Pakistan.

Marketed by:

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L00-01203024