LOSARTAN POTASSIUM + HYDROCHLOROTHIAZIDE

CO-NORMOTEN

50 mg / 12.5 mg Film-Coated Tablet

Angiotensin II Antagonists

FORMULATION

Each film-coated tablet contains:

Losartan Potassium ..... 50 mg

Hydrochlorothiazide ..... 12.5 mg

PRODUCT DESCRIPTION

Losartan Potassium + Hydrochlorothiazide (Co-Normoten) 50 mg / 12.5 mg Film-Coated Tablet is a pinkish red coloured, round, biconvex, film coated tablet.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kinase II)] is a potent vasoconstrictor, the primary vasoactive hormone of the renin angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II selectively blocking the binding of angiotensin II to the AT1 receptor found in the tissues (e.g. Vascular smooth muscle, adrenal gland). There is also an AT2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both Losartan and its principal active metabolite do not exhibit any partial antagonist activity at the AT1 receptor and much greater activity (about 1000 fold) at the AT1 receptor than for the AT2 receptor. In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT1 receptor. The active metabolite is 10 to 40 times more potent by weight than Losartan and appears to be reversible, non-competitive inhibitor of the AT1 receptor. Neither Losartan not its active metabolite inhibits ACE (kinase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin); nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolytes reabsorption, directly increasing excretion of sodium and chloride in approximately equal amounts. Indirectly, the diuretic action of Hydrochlorothiazide reduces plasma volume, with consequent increase in plasma renin activity, increase in aldosterone secretion, increase in urinary potassium loss and decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacokinetics

Following oral administration, Losartan is well absorbed and undergoes substantial first-pass metabolism. The systemic bioavailability of Losartan is approximately 33%. About 14% of an orally administered dose of Losartan is converted to the active metabolite. Mean peak plasma concentrations of Losartan and its metabolite are reached in 1 hour and 3-4 hours respectively. While maximum plasma concentrations of Losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of Losartan. A meal slows absorption of Losartan and decreases its Cmax but has only minor effects on Losartan AUC or on the AUC of the metabolite (about 10% decrease). Both Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Studies in rats indicate that Losartan crosses the Blood-brain barrier poorly, if at all. About 4% of the dose is excreted unchanged in urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the excretion of Losartan and its metabolites. Losartan pharmacokinetics have been investigated in patients<18 years of age, in the elderly (65-75 years) and in both genders. Plasma concentrations of Losartan is about twice as high in female hypertensives then in male hypertensives, but concentrations of the active metabolite are similar in males and females. No dosage adjustments is necessary.

Hydrohlorothiazide is well absorbed. The plasma half-life of Hydrochlorothiazide varies between 5.6 to 14.8 hours. Hydrochlorothiazide crosses the placental but not the blood brain barrier. It is excreted in breast milk. Hydrochlorothiazide is eliminated primarily by renal pathways and 95% of the absorbed dose is excreted in the urine as unchanged drug.

INDICATIONS

It is indicated for the treatment of hypertension, unresponsive to either Losartan Potassium or Hydrochlorothiazide monotherapy.

DOSAGE AND ADMINISTRATION

The usual starting dose for patient whose blood pressure is not adequately controlled by Losartan Potassium or Hydrochlorothiazide monotherapy is one tablet per day. If the blood pressure remains uncontrolled after about three weeks of therapy, the dose may be increased to two tablets per day. More than two tablets per day is not recommended. It may be administered with or without food.

CONTRAINDICATIONS

It is contraindicated in patients who are hypersensitive to Losartan Potassium or Hydrochlorothiazide. Because of Hydrochlorothiazide component, it is contraindicated in patients with anuria or hypersensitivity to other sulphonamide-derived drugs.

It is not recommended for patients with impaired liver function. As a consequences of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individual treated with Losartan Potassium. In some patients these changes were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin aldosterone system (e.g. Patients with severe congestive heart failure), treatment with Losartan Potassium may lead to oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In patients with unilateral or bilateral renal artery stenosis, increase in serum creatinine or blood urea nitrogen (BUN) have been reported with oral administration of Losartan Potassium.

In some patients these changes were reversible upon discontinuation of therapy.

It is not known that Losartan Potassium is excreted in human milk. But significant levels of Losartan and its metabolite were shown in rat milk. Thiazides appear in human milk. Because of the potential of the adverse effects on nursing infants, a decision should be made on whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

No overall differences in effectiveness or safety were observed between elder and younger patients but greater sensitivity of some older individuals cannot be ruled out.

In patients who are intravascularly volume depleted (e.g. those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with Losartan Potassium and Hydrochlorothiazide tablet.

The use of product should be avoided in patients with Systemic Lupus Erythematosus.

Concomitant use of Lithium should be avoided.

WARNINGS AND PRECAUTIONS

Hepatic and Renal Impairment

Losartan Potassium and Hydrochlorothiazide is not recommended for patients with hepatic impairment or severe renal impairment.

As a consequence of inhibiting the renin-angiotensin system, changes inrenal function including renal failure have been reported. These changes in renal function may be reversible upon discontinuation of therapy.

Other medications that affect the renin-angiotensin system including Losartan Potassium and Hydrochlorothiazide may increase blood urea and serum creatinine in patients with bilateral renal artery Stenosis of the artery to a solitary kidney. Similar effects have been reported with Losartan; these changes in renal function may be reversible upon discontinuation of therapy.

Hypotension and Electrolyte/Fluid Imbalance

In patients who are intravenously volume-depleted (e.g. those treated with high dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of Losartan Potassium and Hydrochlorothiazide, or a lower starting dose should be used. Periodic determination of serum electrolyte should be performed at appropriate intervals as in any patients receiving diuretics.

Metabolic and Endocrine Effects

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

Thiazides may decrease urinary calcium excretions 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.

Increase in cholesterol and triglycerides levels may be associated with thiazides diuretic therapy. Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because Losartan decreases uric acid. Losartan in combination with Hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

Other

In patients receiving thiazides, sensitivity reactions may occur with or without a history of allergy of bronchial asthma. Exacerbation or activation of lupus erythematosus has been reported with the use of thiazides.

PREGNANCY AND LACTATION

Pregnancy: When pregnancy is detected, Losartan Poatassium and Hydrochlorothiazide shoud be discontinued as soon as possible. Not to be used in pregnancy as teratogenecity has been shown in experimental animals.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant 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 adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Women of child bearing age should ensure adequate contraception.

Pediatric Use: Safety and efficacy in children has not been established.

DRUG INTERACTIONS

Losartan Potassium does not affect the pharmaceutics or pharmacodynamic of a single dose of Warfarin and also intravenous or oral Digoxin. Coadministration of Losartan Potassium and cimetidine leads to an increase of about 18% in AUC of Losartan Potassium but does not affect the pharmacokinetics of its active metabolite. There is no pharmacokinetic interaction between Losartan Potassium and Hydrochlorothiazide.

When administered concomitantly the drugs, which may interact are: Alcohol, barbiturates or narcotics, antidiabetic drugs, other antihypertensive drugs, cholestyramine and colestipol resins, corticosteroids, pressor amines (e.g. norepinephrine) skeletal muscle relaxants, lithium, Non-Steroidal Anti-inflammatory Drugs (NSAIDS).

ADVERSE EFFECTS

Fixed dose of Losartan Potassium and Hydrochlorothiazide is well tolerated. Adverse events have been limited to those that were reported previously with Losartan Potassium and/or Hydrochlorothiazide. Adverse events are generally mild and transient in nature and do not require discontinuation of therapy. The most commonly reported adverse effects are abdominal pain, edema, swelling, palpitation, back pain, dizziness, cough, sinusitis, upper respiratory tract infection, rash.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".

Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT

Losartan Potassium - Significant lethality was observed on mice and rats, after oral administration of 1000mg/kg and 2000mg/kg of Losartan Potassium respectively. The most likely manifestation of overdosage will be hypotension and tachycardia, bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension occurs, supportive treatment should be instituted.

Hydrochlorothiazide - The oral LD50 of Hydrochlorothiazide is greater than 10g/kg in both mice and rats. The most common signs and symptoms are those caused by electrolyte depletion, such as hypokalemia, hypochloremia, hyponatremia and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia might accentuate cardiac arrythmias. The degree to which Hydrochlorothiazide is removed by hemodialysis has not been established.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY

Losartan Potassium + Hydrochlorothiazide (Co-Normoten) 50 mg / 12.5 mg Film-Coated Tablet - Strip Foil of 10's (Box of 100's) - DRP-2716

DATE OF FIRST AUTHORIZATION

October 30, 2007

DATE OF REVISION

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