For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory xxxxxxxx-8883

TOZAAR-H

(Losartan Potassium and Hydrochlorothiazide Tablets)

COMPOSITION :

Each film coated tablet of Tozaar-H contains :
Losartan Potassium U.S.P. 50 mg
Hydrochlorothiazide U.S.P. 12.5 mg

DESCRIPTION :

Losartan Potassium and Hydrochlorthiazide tablets combine two antihypertensive agents, an angiotensin II receptor (type AT_1) antagonist namely Losartan potassium and a benzothiadiazine diuretic-hydrochlorothiazide.

Losartan Potassium, the first of a new class of antihypertensives is an angiotensin II receptor (type AT_1) antagonist. Chemically it is described as 2-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5yl) (1,1'-biphenyl)-4-yl]methyl]-1H-imidazole-5-methanol. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues (eg. Vascular smooth muscle, adrenal gland). In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT_1 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 AT_1 receptor. Hydrochlorothiazide is a benzothiadiazine diuretic. Thiazides affect renal tubular mechanism of electrolyte reabsorption and increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium.

CLINICAL PHARMACOLOGY :

MECHANISM OF ACTION :

Angiotensin II [formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase 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 by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland). There is also an AT_2 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 agonist activity at the AT_1 receptor and have much greater activity (about 1000 fold) at the AT_1 receptor than for the AT_2 receptor. In vitro binding studies indicate that Losartan is a reversible, competitive inhibitor of the AT_2 receptor. The active metabolite is 10 to 40 times more potent by weight than Losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

Neither Losartan nor its active metabolite inhibits ACE (kininase 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 electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equal 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 coadministration of an angiotensin II antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of antihypertensive action of thiazides is unknown.

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 active metabolite are reached in 1 hour and 3-4 hours respectively. While maximum plasma concentrations of Losartan and its active metab lite 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 C_{max} 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 not been investigated in patients < 18 years of age. Losartan pharmacokinetics has been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of Losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of Losartan are about twice as high in female hypertensives as in male hypertensives, but concentrations of the active metabolite are similar in males and females. No dosage adjustment is necessary.

Hydrochlorothiazide is well absorbed. The plasma half life of Hydrochlorothiazide varies between 5.6 and 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 :

Tozaar-H is indicated for the treatment of hypertension, unresponsive to either Losartan potassium or Hydrochlorothiazide monotherapy.

CONTRAINDICATIONS :

It is contraindicated in patients who are hypersensitive to Losartan potassium or Hydrochlorothiazide. Because of the 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 consequence 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 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.

Safety and effectiveness in Pediatrics has not been established.

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.

WARNING :

Use in Pregnancy :

When used in pregnancy during the second and the third trimester, drugs that at directly on the renin-angiotensin system can cause injury and even death to the developing fetus. Also thiazides cross the placental barrier and appear in cord blood Hence, if administered to pregnant women there is a risk of fetal or neo natal jaundice, thrombocytopenia and possibly other adverse effects that have occurred in adults Therefore when pregnancy is detected, Losartan potassium and Hydrochlorothiazide tablet should be discontiunued as soon as possible.

Female patients of child bearing age should be told about consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told that consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physician as soon as possible.

ADVERSE EFFECTS :

Fixed dose combination 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.

DRUG INTERACTIONS :

Losartan potassium does not affect the pharmacokinetics or pharmacodynamic of a single dose of Warfarin and also of 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. norepinepherine) skeletal muscle relaxants, lithium, Non Steroidal Anti Inflammatory Drugs (NSAIDS).

DOSAGE AND ADMINISTRATION :

The usual starting dose of Losartan potassium and Hydrochlorothiazide tablet for the 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.

OVERDOSAGE :

Losartan potassium : Significant lethality was observed on mice and rats, after oral adminitration 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 LD_{50} 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 dehydrarion resulting from excessive diuresis. If digitalis has also been administered, hypokalemia might accentuate cardiac arrhythmias. The degree to which Hydrochlorothiazide is removed by hemodialysis has not been established.

STORAGE :

Store below 30°C

PRESENTATION :

Tozaar-H is available as pinkish red, round, biconvex, film coated tablets, in strips of 7 &10 tablets.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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