

LOSARZED - H

LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE TABLETS USP

COMPOSITION:

Each Uncoated Tablet Contains:	
Losartan Potassium BP	50 mg
Hydrochlorothiazide USP	12.5 mg
Excipients	q. s.
Colour	Tartrazine

THERAPEUTIC INDICATIONS: Losartan Potassium and hydrochlorothiazide tablets are indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

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 AT1 receptor found in many 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 agonist activity at the AT1 receptor and have much greater affinity (about 1000-fold) for 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 a reversible, non-competitive inhibitor of the AT1 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 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 coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is unknown.

Pharmacodynamics:

- Losartan potassium and Hydrochlorothiazide tablet contains 2 prescription medicines, an angiotensin receptor blocker (ARB) and a diuretic (waterpill). It is used to:
- Lower high blood pressure (hypertension). Losartan potassium and Hydrochlorothiazide tablets is not usually the first medicine used to treat high blood pressure.
- Lower the chance of stroke in patients with high blood pressure and a heart problem called left ventricular hypertrophy (LVH). Losartan potassium and Hydrochlorothiazide tablets may not help Black patients with this problem.

Pharmacokinetics:

- Losartan Potassium:** Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. 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 concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. 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. The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite.
- Hydrochlorothiazide:** Orally administered hydrochlorothiazide is rapidly absorbed and diuretic effect is seen in 1 hour and their duration lasts up to 12-24 hours. These agents are bound to plasma proteins to varying degrees and this has no correlation to their half-life. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours.

Pre-Clinical Safety Data:

- The 3 controlled studies of losartan and hydrochlorothiazide included over 1300 patients assessing the antihypertensive efficacy of various doses of losartan (25, 50 and 100 mg) and concomitant hydrochlorothiazide (6.25, 12.5 and 25 mg). A factorial study compared the combination of losartan/hydrochlorothiazide 50/12.5 mg with its components and placebo. The combination of losartan/hydrochlorothiazide 50/12.5 mg resulted in an approximately additive placebo-adjusted systolic/diastolic response (15.5/9.0 mmHg for the combination compared to 8.5/5.0 mmHg for losartan alone and 7.0/3.0 mmHg for hydrochlorothiazide alone). Another study investigated the dose-response relationship of various doses of hydrochlorothiazide (6.25, 12.5 and 25 mg) or placebo on a background of losartan (50 mg) in patients not adequately controlled (sitting diastolic blood pressure 93-120 mmHg) on losartan (50 mg) alone. The third study investigated the dose-response relationship of various doses of losartan (25, 50 and 100 mg) or placebo on a background of hydrochlorothiazide (25 mg) in patients not adequately controlled (93-120 mmHg) on hydrochlorothiazide (25 mg) alone. These studies showed an added antihypertensive response at trough (24 hours post-dosing) of hydrochlorothiazide 12.5 or 25 mg added to losartan 50 mg of 5.5/3.5 and 10.0/6.0 mmHg, respectively. Similarly, there was an added antihypertensive response at trough when losartan 50 or 100 mg was added to hydrochlorothiazide 25 mg of 9.0/5.5 and 12.5/6.5 mmHg, respectively. There was no significant effect on heart rate. There was no difference in response for men and women or in patients over or under 65 years of age. Black patients had a larger response to hydrochlorothiazide than non-Black patients and a smaller response to losartan. The overall response to the combination was similar for Black and non-Black patients.

POSOLOGY (DOSAGE AND METHOD OF ADMINISTRATION):

Losartan Potassium

- Treatment usually starts with 50 mg Losartan once a day. In some patients the dose may later be increased to 100 mg Losartan once daily. A maximum dose of 150 mg Losartan once daily may be used.
- Hydrochlorothiazide** is effective in doses of 12.5 mg to 50 mg once daily.
- To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with mono therapy.
- The combination may be substituted for the titrated components.

CONTRAINDICATION:

Losartan and hydrochlorothiazide is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

DRUG INTERACTION:

Losartan Potassium:

- Tricyclic antidepressants, antipsychotics, baclofen and amifostine.
- Medicines which retain potassium or may increase potassium levels (e.g. potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamteren, spironolactone] or heparine).
- Non-steroidal anti-inflammatory drugs such as indomethacin, including COX-2-inhibitors.
- ACE (Angiotensin-converting enzyme) inhibitors.
- Lithium containing medicines should not be taken in combination with Losartan without close supervision by your doctor.

Hydrochlorothiazide:

When administered concurrently, the following drugs may interact with thiazide diuretics:

- Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.
- Antidiabetic drugs (oral agents and insulin)
- Other antihypertensive drugs
- Cholestyramine and colestipol resins
- Corticosteroids, ACTH
- Pressor amines (e.g., norepinephrine)
- Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)
- Lithium
- Non-steroidal anti-inflammatory drugs.

ADVERSE/UNDESIRABLE REACTIONS:

Get emergency medical help if you have any of these signs of an allergic reaction: rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing

SIDE EFFECTS:

If you experience the following, stop taking Losartan Hydrochlorothiazide tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:

- A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing). This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients. You may need urgent medical attention or hospitalisation.

Common (may affect up to 1 in 10 people)

- Cough, upper airway infection, congestion in the nose, sinusitis, sinus disorder,
- Diarrhea, abdominal pain, nausea, indigestion,
- Muscle pain or cramps, leg pain, back pain,
- Insomnia, headache, dizziness,
- Weakness, tiredness, chest pain,
- Increased potassium levels (which can cause an abnormal heart rhythm), decreased haemoglobin levels,
- Changes in kidney function including kidney failure,
- Low blood sugar (hypoglycaemia).

SPECIAL WARNINGS AND PRECAUTIONS:

Talk to your doctor or pharmacist before taking Losartan Hydrochlorothiazide tablets if you

- have previously suffered from swelling of the face, lips, throat or tongue
- take diuretics (water pills)
- are on a salt-restricted diet
- have or have had severe vomiting and/or diarrhoea
- have heart failure
- have narrow arteries to your kidneys (renal artery stenosis) or only have one functioning kidney, or you have recently had a kidney transplant
- have narrowing of the arteries (atherosclerosis), angina pectoris (chest pain due to poor heart function)
- have 'aortic or mitral valve stenosis' (narrowing of the valves of the heart) or 'hypertrophic cardiomyopathy' (a disease causing thickening of heart muscle)
- have a history of mild to moderate liver impairment
- are diabetic
- have had gout
- have or have had an allergic condition, asthma or a condition that causes joint pain, skin rashes and fever (systemic lupus erythematosus)
- have high calcium or low potassium levels or you are on a low potassium diet
- need to have an anaesthetic (even at the dentist) or before surgery, or if you are going to have tests to check your parathyroid function, you must tell the doctor or medical staff that you are taking Losartan Hydrochlorothiazide tablets.
- Suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland).
- are taking any of the following medicines used to treat high blood pressure:- an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems-alkisiren
- PREGNANCY AND BREAST-FEEDING:** Losartan Hydrochlorothiazide tablets are not recommended during pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy. Losartan Hydrochlorothiazide tablets are not recommended for mothers who are breast-feeding.

SYMPTOMS OF OVER-DOSAGE AND ITS TREATMENT:

If you accidentally take more tablets than you should, tell a doctor or get other medical advice straight away. Take the medicine pack with you.

Losartan Potassium Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m² basis. Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide: The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats. 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. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

LOSARZED-H is Yellow colour, round shape, standard biconvex film coated tablet, plain on both side.

IMPORTANT INFORMATION ABOUT THE EXCIPIENTS OF LOSARZED-H TABLETS:

LOSARZED - H Contains microcrystalline cellulose, anhydrous calcium hydrogen phosphate, colloidal silicon dioxide, Purified Talc, magnesium stearate, purified talc and color coat Tartrazine yellow.

STORAGE: Store below 30°C. Protected from the moisture. Keep out of the reach and sight of children.

PRESENTATION:

LOSARZED - H: An Alu Alu blister of 10 tablets,

MFG. LIC. NO.: G/25/1905

SHELF LIFE: 36 Months

If you have any comments on the way this leaflet is written, please contact Medical Information at Zota Healthcare Limited,

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