



adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo.

In general, treatment with losartan potassium–hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as drug related that occurred with an incidence greater than placebo in one percent or more of patients treated with losartan potassium–hydrochlorothiazide.

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, was generally well tolerated. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

The following additional adverse reactions have been reported in post-marketing experience with Losartan Potassium & Hydrochlorothiazide and/or in clinical trials or post-marketing use with the individual components:

Neoplasms Benign, malignant and unspecified (incl cysts and polyps): Non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma).

Blood and the lymphatic system disorders: Thrombocytopenia, anemia, aplastic anemia, hemolytic anemia, leukopenia, agranulocytosis.

Immune system disorders: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors.

Metabolism and nutrition disorders: Anorexia, hyperglycemia, hyperuricemia, electrolyte imbalance including hyponatremia and hypokalemia.

Psychiatric disorders: Insomnia, restlessness

Nervous system disorders: Dysgeusia, headache, migraine, paraesthesias.

Eye disorders: Xanthopsia, transient blurred vision. Frequency 'not known'. Choroidal effusion, acute myopia, acute angle-closure glaucoma

Cardiac disorders: Palpitation, tachycardia.

Vascular disorders: Dose-related orthostatic effects, necrotizing angitis (vasculitis) (cutaneous vasculitis).

Respiratory, thoracic and mediastinal disorders: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress, pneumonitis and pulmonary edema. Acute

respiratory distress has been reported in very rare instances (see PRECAUTIONS).

Gastrointestinal disorders: Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhea, constipation, nausea, vomiting, pancreatitis, sialoadenitis.

Hepato-biliary disorders: Hepatitis, jaundice (intrahepatic cholestatic jaundice).

Skin and subcutaneous tissue disorders: Rash, pruritus, purpura (including Henoch-Schoenlein purpura), toxic epidermal necrolysis, urticaria, erythroderma, photosensitivity, cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders: Back pain, muscle cramps, muscle spasm, myalgia, arthralgia.

Renal and urinary disorders: Glycosuria, renal dysfunction, interstitial nephritis, renal failure.

Reproductive system and breast disorders: Erectile dysfunction/impotence.

General disorders and administration site conditions: Chest pain, edema/swelling, malaise, fever, weakness.

Investigations: Liver function abnormalities.

Description of Selected Side Effects Non-melanoma skin cancer (NMSC):Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide (HCTZ) and NMSC has been observed.

One study included a population comprised of 71,533 cases of BCC and 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted odds ratio (OR) of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose-response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (95% CI: 3.0-4.9) for high use (~ 25,000 mg) and OR 7.7 (95% CI: 5.7- 10.5) for the highest cumulative dose (~ 100,000 mg).

OVERDOSE

No specific information is available on the treatment of overdose with Presartan H. Treatment is symptomatic and supportive. Therapy with Presartan H should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan

Limited data are available in regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan potassium nor the active metabolite can be removed

by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hyponatremia, 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Losartan

Losartan inhibits systolic and diastolic pressor responses to angiotensin II infusions. At peak, 100 mg of losartan potassium inhibits these responses by approximately 65%; 24 hours after single and multiple-dose administration, inhibition is about 26-39%.

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. During chronic (6 weeks) treatment of hypertensive patients with 100 mg/day losartan, approximately 2-3 fold increases of plasma angiotensin II were observed at time of peak plasma drug concentrations. In some patients, greater increases were observed, particularly during short term (2 weeks) treatment. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent at 2 and 6 weeks, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days. Effects of Losartan Potassium & Hydrochlorothiazide on PRA and angiotensin II levels were similar to those observed with 50 mg of losartan.

Since losartan is a specific antagonist of the angiotensin II receptor type AT₁, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. In a study which compared the effects of 20 mg and 100 mg of losartan potassium and an ACE inhibitor on responses to angiotensin I, angiotensin II and bradykinin, losartan was shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin. This finding is consistent with losartan's specific mechanism of action. In contrast, the ACE inhibitor was shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

Plasma concentrations of losartan and its active metabolite and the antihypertensive effect of losartan increase with increasing dose. Since losartan and its active metabolite are both angiotensin II receptor antagonists, they both contribute to the antihypertensive effect.

In a single-dose study in normal males, the administration of 100 mg of losartan potassium, under dietary high- and low-salt conditions,

did not alter glomerular filtration rate, effective renal plasma flow or filtration fraction. Losartan had a natriuretic effect which was more pronounced on a low-salt diet and did not appear to be related to inhibition of early proximal reabsorption of sodium. Losartan also caused a transient increase in urinary uric acid excretion.

In nondiabetic hypertensive patients with proteinuria (≥2 g/24 hours) treated for 8 weeks, the administration of losartan potassium 50 mg titrated to 100 mg significantly reduced proteinuria by 42%.

Fractional excretion of albumin and IgG also was significantly reduced. In these patients, losartan maintained glomerular filtration rate and reduced filtration fraction.

In postmenopausal hypertensive women treated for 4 weeks, 50 mg of losartan potassium had no effect on renal or systemic prostaglandin levels. Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

Losartan potassium, administered in doses of up to 150 mg once daily, did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL-cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

Generally losartan caused a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent with chronic therapy. In controlled clinical trials in hypertensive patients, no patients were discontinued due to increases in serum creatinine or serum potassium.

In a 12-week, parallel-design study in patients with left ventricular failure (New York Heart Association Functional Classes II-IV), most of whom were receiving diuretics and/or digitalis, losartan potassium administered in once-daily doses of 2.5, 10, 25 and 50 mg was compared to placebo. The 25-mg and 50-mg doses produced positive hemodynamic and neurohormonal effects which were maintained for the length of the study. Hemodynamic responses were characterized by an increase in cardiac index and decreases in: pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate. The occurrence of hypotension was dose related in these heart failure patients. Neurohormonal results were characterized by a reduction in circulating levels of aldosterone and norepinephrine.

Pharmacokinetic properties

Absorption

Losartan

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin.

The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism

Losartan

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ¹⁴C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan

Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ¹⁴C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous dose of ¹⁴C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

Characteristics in Patients

Losartan-Hydrochlorothiazide

The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan

The plasma concentrations of losartan and its active metabolite in elderly hypertensives are not significantly different from those in young hypertensives.

Plasma concentrations of losartan were up to 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females. This apparent pharmacokinetic difference is not judged to be of clinical significance.

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7- fold greater than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above

10 mL/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in hemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor the active metabolite can be removed by hemodialysis.

STORAGE

Store below 30°C, in a dry place
JAUHKAN DARIPADA KANAK-KANAK
KEEP OUT OF REACH OF CHILDREN

PRESENTATION

Alu-Alu blister of 14 tablets. Pack of 28's tablets per box

SHELF LIFE

24 Months

DATE OF REVISION

November 2022

Product Registration Holder

The Zyfas Medical Co.
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Taman Perindustrian Nusa Cemerlang,
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Size: 480 x 150 mm