LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE- losartan potassium and hydrochlorothiazide tablet, film coated
Direct Rx

LOSARTAN POTASSIUM/HCTZ

1.1 Hypertension

Losartan potassium and hydrochlorothiazide tablets are indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure lowers the risk of fatal and non-fatal cardiovascular (CV) events, primarily strokes and myocardial infarction. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including losartan and hydrochlorothiazide.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than 1 drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in Black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients [see Clinical Studies (14) and Dosage and Administration (2.1)].

Losartan potassium and hydrochlorothiazide tablets may be administered with other antihypertensive agents.

1.2 Hypertensive Patients with Left Ventricular Hypertrophy

Losartan potassium and hydrochlorothiazide tablets are indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients. [See Use in Specific Populations (8.6), Clinical Pharmacology (12.3), and Dosage and Administration (2.2).]

2.1 Hypertension

The usual starting dose of losartan potassium and hydrochlorothiazide tablets is 50/12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. The dosage can be increased after 3 weeks of therapy to a maximum of 100/25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily as needed to control blood pressure [see Clinical Studies (14.2)].

Initiate a patient whose blood pressure is not adequately controlled with losartan 50 mg monotherapy with losartan potassium and hydrochlorothiazide tablets 50/12.5 once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dosage may be increased to two tablets of losartan potassium and hydrochlorothiazide tablets 50/12.5 once daily or one tablet of losartan potassium and hydrochlorothiazide tablets 100/25 once daily.

Initiate a patient whose blood pressure is not adequately controlled with losartan 100 mg monotherapy with losartan potassium and hydrochlorothiazide tablets 100/12.5 (losartan 100 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, increase the dose to two tablets of losartan potassium and hydrochlorothiazide tablets 50/12.5 once daily or one tablet of losartan potassium and hydrochlorothiazide tablets 100/25 once daily.

Initiate a patient whose blood pressure is inadequately controlled with hydrochlorothiazide 25 mg once daily, or is controlled but who experiences hypokalemia with this regimen, on losartan potassium and hydrochlorothiazide tablets 50/12.5 once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. Evaluate the clinical response to losartan potassium and hydrochlorothiazide tablets 50/12.5 and, if blood pressure remains uncontrolled after about 3 weeks of therapy, increase the dose to two tablets of losartan potassium and hydrochlorothiazide tablets 50/12.5 once daily or one tablet of losartan potassium and hydrochlorothiazide tablets 100/25 once daily.

2.2 Hypertensive Patients with Left Ventricular Hypertrophy

In patients whose blood pressure is not adequately controlled on 50 mg losartan potassium, initiate treatment with losartan potassium and hydrochlorothiazide tablets 50/12.5. If additional blood pressure reduction is needed, increase the dose to losartan potassium and hydrochlorothiazide tablets 100/12.5, followed by losartan potassium and hydrochlorothiazide tablets 100/25. For further blood pressure reduction add other antihypertensives [see Clinical Studies (14)].

Losartan potassium and hydrochlorothiazide tablets, USP 50/12.5 are yellow, capsule-shaped, film-coated tablets, debossed with “HH” on one side and “211” on the other side.

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Losartan potassium and hydrochlorothiazide tablets, USP 100/12.5 are white to off-white, capsule-shaped, film-coated tablets, debossed with “HH” on one side and “213” on the other side.

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Losartan potassium and hydrochlorothiazide tablets, USP 100/25 are yellow, capsule-

shaped, film-coated tablets, debossed with “HH” on one side and “212” on the other side.

Losartan potassium and hydrochlorothiazide tablets are contraindicated:

- In patients who are hypersensitive to any component of this product.
- In patients with anuria
- For coadministration with aliskiren in patients with diabetes

5.1 Fetal Toxicity

Losartan potassium and hydrochlorothiazide tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue losartan potassium and hydrochlorothiazide tablets as soon as possible.

Thiazides cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice, thrombocytopenia [see Use in Specific Populations (8.1)].

5.2 Hypotension in Volume-or Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume-or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of treatment with losartan potassium and hydrochlorothiazide tablets. Correct volume or salt depletion prior to administration of losartan potassium and hydrochlorothiazide tablets. Do not use losartan potassium and hydrochlorothiazide tablets as initial therapy in patients with intravascular volume depletion.

5.3 Impaired Renal Function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on losartan potassium and hydrochlorothiazide tablets. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on losartan potassium and hydrochlorothiazide tablets [see Drug Interactions (7.3) and Use in Specific Populations (8.8)].

5.4 Hypersensitivity

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

5.5 Electrolyte and Metabolic Effects

In double-blind clinical trials of various doses of losartan potassium and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 6.7% versus 3.5% for placebo; the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% versus 0% for placebo.

Losartan potassium and hydrochlorothiazide tablets contain hydrochlorothiazide which can cause hypokalemia, hyponatremia and hypomagnesemia. Hypomagnesemia can result in hypokalemia which may be difficult to treat despite potassium repletion. Losartan potassium and hydrochlorothiazide tablets also contain losartan which can cause hyperkalemia. Monitor serum electrolytes periodically [see Drug Interactions (7.1)].

Concomitant use of other drugs that may increase serum potassium may lead to hyperkalemia [see Drug Interactions (7.1)].

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hyperuricemia may occur or frank gout may be precipitated in patients receiving thiazide therapy. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels.

5.6 Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

5.7 Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Losartan potassium-hydrochlorothiazide has been evaluated for safety in 858 patients treated for essential hypertension and 3889 patients treated for hypertension and left ventricular hypertrophy. Most adverse reactions have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse events was required in only 2.8% and 2.3% of patients treated with the combination and placebo, respectively.

In these double-blind controlled clinical trials, adverse reactions occurring in greater than 2% of subjects treated with losartan-hydrochlorothiazide and at a greater rate than

placebo were: back pain (2.1% vs 0.6%), dizziness (5.7% vs 2.9%), and upper respiratory infection (6.1% vs 4.6%).

The following additional adverse reactions have been reported in clinical trials with losartan potassium and hydrochlorothiazide tablets and/or the individual components:

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

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.

Cardiac disorders: Palpitation, tachycardia.

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

Respiratory, thoracic and mediastinal disorders: Nasal congestion.

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

Hepato-biliary disorders: Jaundice (intrahepatic cholestatic jaundice).

Skin and subcutaneous tissue disorders: Rash, pruritus, purpura, toxic epidermal necrolysis, urticaria, photosensitivity, cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders: Muscle cramps, muscle spasm.

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, malaise, weakness.

Investigations: Liver function abnormalities.

Cough

Persistent dry cough has been associated with ACE-inhibitor use and in practice can be a cause of discontinuation of ACE-inhibitor therapy. Two prospective, parallel-group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE-inhibitor therapy. Patients who had typical ACE-inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown in Table 1 below.

Table 1:

Study 1*

HCTZ

Losartan

Lisinopril

Cough

25%

17%

69%

Study 2†

Placebo

Losartan

Lisinopril

Cough

35%

29%

62%

* Demographics = (89% Caucasian, 64% female)

† Demographics = (90% Caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE-inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in postmarketing experience.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of losartan potassium and hydrochlorothiazide tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Digestive: Hepatitis has been reported rarely in patients treated with losartan.

Hematologic: Thrombocytopenia.

Hypersensitivity: 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. Vasculitis, including Henoch-Schönlein purpura, has been reported with losartan. Anaphylactic reactions have been reported.

Musculoskeletal: Rhabdomyolysis.

Skin: Erythroderma.

Non-melanoma Skin Cancer: Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

7.1 Agents Increasing Serum Potassium

Coadministration of losartan with other drugs that raise serum potassium levels may result in hyperkalemia. Monitor serum potassium in such patients.

7.2 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported with concomitant use of angiotensin II receptor antagonists or thiazide diuretics. Monitor lithium levels in patients receiving losartan potassium and hydrochlorothiazide tablets and lithium.

7.3 Non-Steroidal Anti-Inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors

Losartan Potassium

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists (including losartan) may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving losartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Hydrochlorothiazide

The administration of a non-steroidal anti-inflammatory agent including a selective COX-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when losartan potassium and hydrochlorothiazide tablets and non-steroidal anti-inflammatory agents including selective COX-2 inhibitors are used concomitantly, observe closely to determine if the desired effect of the diuretic is obtained.

In patients receiving diuretic therapy, coadministration of NSAIDs with angiotensin receptor blockers, including losartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving hydrochlorothiazide, losartan, and NSAID therapy.

7.4 Dual Blockade of the Renin-Angiotensin System (RAS)

Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) trial enrolled 1448 patients with type 2 diabetes, elevated urinary-albumin-to-creatinine ratio, and decreased estimated glomerular filtration rate (GFR 30 to 89.9 mL/min), randomized them to lisinopril or placebo on a background of losartan therapy and followed them for a median of 2.2 years. Patients receiving the combination of losartan and lisinopril did not obtain any additional benefit compared to monotherapy for the combined endpoint of decline in GFR, end-stage renal disease, or death, but experienced an increased incidence of hyperkalemia and acute kidney injury compared with the monotherapy group.

Closely monitor blood pressure, renal function, and electrolytes in patients on losartan potassium and hydrochlorothiazide tablets and other agents that affect the RAS.

Do not coadminister aliskiren with losartan potassium and hydrochlorothiazide tablets in patients with diabetes. Avoid use of aliskiren with losartan potassium and hydrochlorothiazide tablets in patients with renal impairment (GFR <60 mL/min).

7.5 The Use of Hydrochlorothiazide with Other Drugs

When administered concurrently, the following drugs may interact with thiazide diuretics [see Clinical Pharmacology (12.3)]:

Antidiabetic drugs (oral agents and insulin) — dosage adjustment of the antidiabetic drug may be required.

Cholestyramine and colestipol resins — Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. Stagger the dosage of hydrochlorothiazide and the resin such that hydrochlorothiazide is administered at least 4 hours before or 4 to 6 hours after the administration of the resin.

8.1 Pregnancy

Risk Summary

Losartan potassium and hydrochlorothiazide tablets can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. When pregnancy is detected, discontinue losartan potassium and hydrochlorothiazide tablets as soon as possible (see Clinical Considerations).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease associated Maternal and/or Embryo/Fetal Risk Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, post-partum hemorrhage).

Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Losartan:

Use of drugs that act on the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue losartan potassium and hydrochlorothiazide tablets, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to losartan potassium and hydrochlorothiazide tablets for hypotension, oliguria, and hyperkalemia. In neonates with a history of in utero exposure to losartan potassium and hydrochlorothiazide tablets, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Hydrochlorothiazide:

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma. Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not alter the course of pre-eclampsia, these drugs should not be used to treat hypertension in pregnant women. The use of hydrochlorothiazide for other indications in pregnancy should be avoided.

Data

Animal Data

There was no evidence of teratogenicity in rats or rabbits treated with a maximum losartan potassium dose of 10 mg/kg/day in combination with 2.5 mg/kg/day of hydrochlorothiazide. At these dosages, respective exposures (AUCs) of losartan, its active metabolite, and hydrochlorothiazide in rabbits were approximately 5, 1.5, and 1.0 times those achieved in humans with 100 mg losartan in combination with 25 mg hydrochlorothiazide. AUC values for losartan, its active metabolite and hydrochlorothiazide, extrapolated from data obtained with losartan administered to rats at a dose of 50 mg/kg/day in combination with 12.5 mg/kg/day of hydrochlorothiazide, were approximately 6, 2, and 2 times greater than those achieved in humans with 100 mg of losartan in combination with 25 mg of hydrochlorothiazide. Fetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs, was observed when females were treated prior to and throughout gestation with 10 mg/kg/day losartan in combination with 2.5 mg/kg/day hydrochlorothiazide. As also observed in studies with

losartan alone, adverse fetal and neonatal effects, including decreased body weight, renal toxicity, and mortality, occurred when pregnant rats were treated during late gestation and/or lactation with 50 mg/kg/day losartan in combination with 12.5 mg/kg/day hydrochlorothiazide. Respective AUCs for losartan, its active metabolite and hydrochlorothiazide at these dosages in rats were approximately 35, 10 and 10 times greater than those achieved in humans with the administration of 100 mg of losartan in combination with 25 mg hydrochlorothiazide. When hydrochlorothiazide was administered without losartan to pregnant mice and rats during their respective periods of major organogenesis, at doses up to 3000 and 1000 mg/kg/day, respectively, there was no evidence of harm to the fetus.

8.2 Lactation

Risk Summary

It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of losartan potassium and hydrochlorothiazide tablets in pediatric patients have not been established.

Neonates with a history of in utero exposure to losartan potassium and hydrochlorothiazide tablets: If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

8.5 Geriatric Use

In a controlled clinical study for the reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy, 2857 patients (62%) were 65 years and over, while 808 patients (18%) were 75 years and over. In an effort to control blood pressure in this study, patients were coadministered losartan and hydrochlorothiazide 74% of the total time they were on study drug. No overall differences in effectiveness were observed between these patients and younger patients. Adverse events were somewhat more frequent in the elderly compared to non-elderly patients for both the losartan-hydrochlorothiazide and the control groups [see Clinical Pharmacology (12.3)].

8.6 Race

In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, Black patients with hypertension and left ventricular hypertrophy treated with atenolol had a lower risk of stroke, the primary composite endpoint, as compared with Black patients treated with losartan (both cotreated with hydrochlorothiazide in the majority of patients). In the subgroup of Black patients (n=533, 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 26 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 42 per 1000 patient-years) on losartan. This finding could not be explained on the basis of differences in the populations other than race or on any imbalances between treatment groups. In

addition, blood pressure reductions in both treatment groups were consistent between Black and non-Black patients. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study provides no evidence that the benefits of losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Initiation of losartan potassium and hydrochlorothiazide tablets is not recommended for patients with hepatic impairment because the appropriate starting dose of losartan, 25 mg, is not available.

8.8 Renal Impairment

Changes in renal function have been reported in susceptible individuals [see Dosage and Administration (2.1), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)]. Safety and effectiveness of losartan potassium and hydrochlorothiazide tablets in patients with severe renal impairment (creatinine clearance <30 mL/min) have not been established.

Losartan potassium and hydrochlorothiazide tablets, 50/12.5 mg, losartan potassium and hydrochlorothiazide tablets, 100/12.5 mg and losartan potassium and hydrochlorothiazide tablets, 100/25 mg combine an angiotensin II receptor blocker acting on the AT1 receptor subtype and a diuretic, hydrochlorothiazide.

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. Its empirical formula is $C_{22}H_{22}ClKN_6O$, and its structural formula is:

73c71ed3-figure-01
Losartan potassium is a white to off-white free-flowing crystalline powder with a molecular weight of 461.01. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

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

73c71ed3-figure-02
Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

Losartan potassium and hydrochlorothiazide tablets, USP are available for oral administration in three tablet combinations of losartan and hydrochlorothiazide. Losartan potassium and hydrochlorothiazide tablets 50/12.5 mg contain 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. Losartan potassium and hydrochlorothiazide tablets 100/12.5 mg contain 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. Losartan potassium and hydrochlorothiazide tablets 100/25 mg contain 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. Inactive ingredients are microcrystalline cellulose, lactose monohydrate, pregelatinized starch, magnesium stearate, colloidal silicon dioxide, hydroxypropyl cellulose,

hypromellose, and titanium dioxide. Losartan potassium and hydrochlorothiazide tablets 50/12.5 mg and 100/25 mg also contain D&C yellow No. 10 aluminum lake and FD&C blue No. 1/brilliant blue FCF aluminum lake.

Losartan potassium and hydrochlorothiazide tablets 50/12.5 mg contain 4.24 mg (0.108 mEq) of potassium, losartan potassium and hydrochlorothiazide tablets 100/12.5 mg contain 8.48 mg (0.216 mEq) of potassium, and losartan potassium and hydrochlorothiazide tablets 100/25 mg contain 8.48 mg (0.216 mEq) of potassium.

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.

Losartan potassium and hydrochlorothiazide tablets, USP are supplied as a film-coated tablet.

Losartan/ Hydrochlorothiazide

Color

Shape

Engraving

NDC 43547-xxx-xx

Bottle/ 30

Bottle/ 90

Bottle/ 1000

50/12.5 mg

yellow

capsule-shaped

HH/211

423-03

423-09

423-11

100/12.5 mg

white to off-white

capsule-shaped

HH/213

425-03

425-09

425-11

100/25 mg

yellow

capsule-shaped

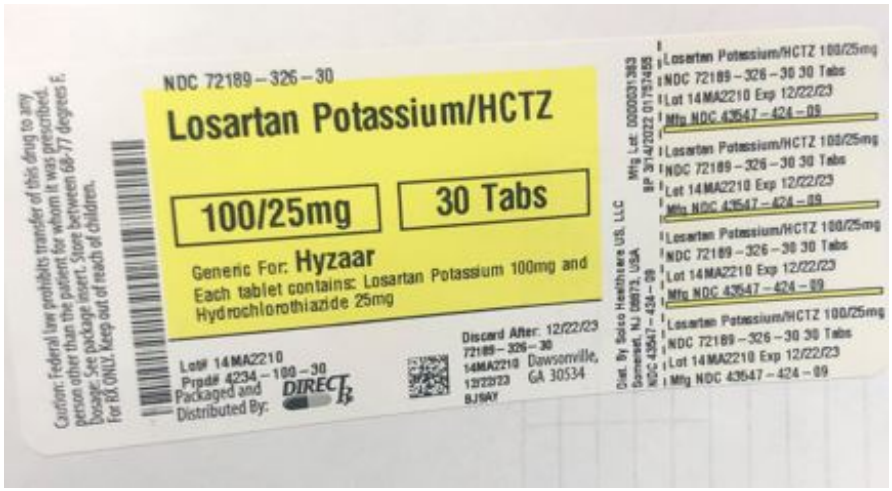
HH/212

424-03

424-09

424-11

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.



LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE

losartan potassium and hydrochlorothiazide tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72189-326(NDC:43547-424)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

LOSARTAN POTASSIUM (UNII: 3ST302B24A) (LOSARTAN - UNII:JMS50MPO89)	LOSARTAN POTASSIUM	100 mg
HYDROCHLOROTHIAZIDE (UNII: 0J48LPH2TH) (HYDROCHLOROTHIAZIDE - UNII:0J48LPH2TH)	HYDROCHLOROTHIAZIDE	25 mg

Inactive Ingredients

Ingredient Name	Strength
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
STARCH, CORN (UNII: O8232NY3SJ)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYDROXYPROPYL CELLULOSE (1600000 WAMW) (UNII: RFW2ET671P)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	yellow	**Score**	no score
Shape	CAPSULE	**Size**	15mm
Flavor		**Imprint Code**	HH;212
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72189-326-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	02/21/2022	
2	NDC:72189-326-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/21/2022	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204901	02/21/2022	

Labeler - Direct Rx (079254320)

Registrant - Direct Rx (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
Direct Rx		079254320	relabel(72189-326)