Losartan potassium + Hydrochlorothiazide

Combizar®

Rx

50 mg/ 12.5 mg & 100 mg/ 25 mg Film-coated Tablet

Angiotensin II Antagonist / Diuretic

FORMULATION
Each film-coated tablet contains:
Losartan potassium..... 50 mg
Hydrochlorothiazide..... 12.5 mg
or
Losartan potassium..... 100 mg
Hydrochlorothiazide..... 25 mg

PRODUCT DESCRIPTION
Losartan potassium + Hydrochlorothiazide (Combizar®) 50 mg/12.5 mg Tablet: Yellow, odd-shaped, film-coated tablet, bisected on one side and plain on the other side
Losartan potassium + Hydrochlorothiazide (Combizar®) 100 mg/25 mg Tablet: Golden yellow, oval, film-coated tablet, biconvex, bisected on one side and plain on the other side

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
The blood pressure lowering effect of losartan is additive with that of hydrochlorothiazide (HCTZ), decreasing blood pressure to a greater degree than either component alone.

Losartan potassium
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 angiotensin II subtype 1 (AT_1) receptor found in many tissues such as vascular smooth muscles, adrenal gland, kidneys, and the heart. A second angiotensin II receptor has been identified as the AT_2 receptor subtype found in many tissues but 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 affinity (about 1000-fold) for the AT_1 receptor than that for the AT_2 receptor. *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 a reversible, non-competitive inhibitor of the AT_1 receptor.

Losartan does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin). Angiotensin II receptor antagonism results in dose-related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Hydrochlorothiazide
Hydrochlorothiazide (HCTZ), a thiazide diuretic, increases the excretion of water by inhibiting the reabsorption of sodium and chloride ions at the distal renal tubule. The natriuretic effects are accompanied by a secondary loss of potassium and bicarbonate which can cause a mild hypokalemic, hypochloremic, metabolic alkalosis. Thiazides also decrease the elimination of calcium and uric acid. Thiazide diuretics usually do not affect normal blood pressure. When chronically administered, thiazide diuretics decrease peripheral vascular resistance. The exact mechanism responsible for lowered peripheral resistance is not known, however, excretion of urinary sodium by the kidneys is required to achieve blood pressure reduction.

Indirectly, the diuretic action of HCTZ reduces plasma volume, with consequent increases in plasma renin activity, aldosterone secretion, urinary potassium loss, and decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, therefore coadminstration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with HCTZ.

Diuresis begins with 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours after oral administration of HCTZ.

PHARMACOKINETICS
Losartan potassium
Losartan is well absorbed after oral administration. It undergoes presystemic metabolism, forming an active metabolite (E-3174) and other inactive metabolites. Systemic bioavailability of losartan tablets is about 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3 to 4 hours, respectively. There is no clinically significant effect on the plasma concentration profile of losartan when the drug is administered with a meal.

Both losartan and its metabolite are highly bound (≥99%) to plasma proteins, primarily albumin. Losartan's volume of distribution is 34 L.

Plasma concentrations of the active metabolite are higher than those of losartan at all doses, C_{max} and AUC for E-3174 are about 2 and 5 to 8 times greater than the corresponding values for losartan itself.

After oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with terminal half-lives of about 2 hours (1.5 to 2.5 hours) and 6 to 9 hours, respectively. As anticipated from their short half-lives, neither losartan nor its active metabolite accumulates significantly in plasma during once-daily dosing with 100 mg.

The plasma clearance of losartan and its active metabolite is approximately 600 mL/min and 50 mL/min, respectively. Losartan is extensively metabolized in the liver. Approximately 35% of an oral losartan dose is excreted in urine as unchanged compound and metabolites. Only 4% of the dose is eliminated unchanged via the kidneys. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. Losartan and its metabolites are also eliminated by biliary excretion, with 58% of an oral dose recovered in the feces.

Hydrochlorothiazide
HCTZ is well absorbed from the gastrointestinal tract. Oral bioavailability is approximately 65 to 75%. After oral administration of HCTZ at doses of 12.5 to 100 mg, peak plasma concentrations of 70 to 490 ng/mL are observed within 1 to 5 hours of dosing.

Approximately 40 to 60% of the drug is bound to plasma proteins. HCTZ crosses the placenta, but not the blood-brain barrier and is distributed in breast milk. It appears to be preferentially bound to red blood cells.

HCTZ is not metabolized but is eliminated rapidly as unchanged drug in the urine. HCTZ's plasma half-life ranged from 5.6 to 15 hours when plasma levels were followed for at least 24 hours. At least 61% of an oral dose is eliminated unchanged within 24 hours.

Special Populations:
Renal Impairment
Plasma concentrations and AUCs of losartan and its active metabolite are increased by 50 to 90% in patients with mild (creatinine clearance 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal impairment. Renal clearance was reduced by 55 to 85% for both losartan and its active metabolite in these patients.

In patients with renal impairment (mean creatinine clearance of 19 mL/min), the elimination half-life of HCTZ was prolonged to 20.7 hours.

Hepatic Impairment
In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma concentrations of losartan and its active metabolite were 5 and 1.7 times higher than in healthy subjects, respectively. Losartan has not been studied in patients with severe hepatic impairment.

Monitor patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

INDICATION
Treatment of hypertension; for patients in whom combination therapy is appropriate.

DOSAGE AND ADMINISTRATION
Usual Initial & Maintenance Adult Dose: 1 tablet of Losartan 50 mg + HCTZ 12.5 mg FDC once daily.
- For patients who do not respond adequately, adjust to a maximum dose of:
  1 tablet of Losartan 100 mg + HCTZ 25 mg FDC daily or,
  2 tablets of Losartan 50 mg + HCTZ 12.5 mg FDC daily
- In general, the antihypertensive effect is attained within 3 weeks after initiation of therapy.
  Or, as prescribed by the physician.

CONTRAINDICATIONS
- Hypersensitivity to losartan potassium, HCTZ, other sulfonamide derivatives, or to any component of the product
- Therapy resistant hypokalemia or hypercalcemia
- Severe hepatic impairment, cholestasis and biliary obstructive disorders
- Refractory hyponatremia
- Symptomatic hyperuricemia/gout
- Pregnancy
- Severe renal impairment (creatinine clearance <30 mL/min)
- Anuria
- Concomitant use with aliskiren in patients with diabetes mellitus or renal impairment [glomerular filtration rate (GFR) <60 mL/min/1.73 m^2]

WARNINGS AND PRECAUTIONS

Fetal Toxicity: When pregnancy is detected, discontinue losartan potassium as soon as possible. Drugs that act directly on the renin-angiotensin-aldosterone system can cause injury and death to the developing fetus.

Losartan potassium
Fetal toxicity: The use of drugs that act on the renin-angiotensin-aldosterone 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 as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin-aldosterone system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin-aldosterone system for a particular patient, the mother should be informed of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue losartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. However, physicians and patients should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to losartan for hypotension, oliguria and hyperkalemia.

Infants with history of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Hypersensitivity: Angioedema (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. Patients with history of angioedema should be closely monitored (see **Undesirable Effects**).

Hypotension and Electrolyte/Fluid Imbalance: Symptomatic hypotension may be observed in patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics). These conditions should be corrected before starting losartan therapy, or a lower starting dose should be used.

Monitor serum potassium levels in type 2 diabetic patients with nephropathy treated with an angiotensin II antagonist. Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended.

Renal Impairment: Due to inhibition of the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been seen in susceptible patients (e.g., patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency, pre-existing renal dysfunction or volume depletion) treated with losartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function.

As with other drugs affecting the renin-angiotensin-aldosterone system, increases in blood urea nitrogen (BUN) and serum creatinine have been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been observed with losartan; these effects may be reversible upon discontinuation of therapy in some patients.

There is no experience with losartan in patients with recent kidney transplantation.

Hepatic Impairment: In patients with a history of hepatic impairment, a lower dose of losartan should be given since significantly increased plasma concentrations of the drug in cirrhotic patients has been observed in pharmacokinetic studies. There is no therapeutic experience with losartan in patients with severe hepatic impairment; thus, losartan should not be administered in patients with severe hepatic impairment.

Primary hyperaldosteronism: Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of losartan is not recommended.

Coronary Heart Disease and Cererbrovascular Disease: As with any antihypertensive agent, excessive hypotension in patients with ischemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart Failure: There is a risk of severe arterial hypotension and (often acute) renal impairment in patients with heart failure with or without renal impairment.

Aortic and Mitral Valve Stenosis, Obstructive Hypertrophic Cardiomyopathy: Special caution is indicated in patients with aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Race: In the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of losartan on cardiovascular morbidity and mortality compared with atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively reduced blood pressure in Black patients. In the overall LIFE study population, treatment with losartan resulted in a 13% risk reduction compared with atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. Losartan reduced the risk of cardiovascular morbidity and mortality compared with atenolol in non-Black, hypertensive patients with left ventricular hypertrophy as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. However, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan.

Hydrochlorothiazide
Fluid/Electrolyte Imbalance: Serum electrolytes should be monitored regularly. Patients should be observed for clinical signs of fluid or electrolyte imbalance (e.g., volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia, or hypokalemia). Warning signs or symptoms of fluid and electrolyte imbalance include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances including nausea and vomiting.

Hypokalemia may develop, particularly with brisk diuresis, when liver cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment, except under extraordinary situations (e.g., liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyonatremia may be seen in edematous patients in hot weather. Appropriate treatment is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. Appropriate replacement therapy is the treatment of choice in actual salt depletion.

Renal Impairment: Use with caution in patients with renal disease resulting in severe renal impairment because HCTZ decreases glomerular filtration rate and may precipitate azotemia

Hepatic Impairment: Use with caution in patients with hepatic disease or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity: Hypersensitivity reactions to HCTZ may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. As a sulfonamide derivative, HCTZ can cause skin rashes and blood dyscrasias.

Systemic Lupus Erythematosus: Exacerbation or activation of systemic lupus erythematosus has been associated with the use of thiazide diuretics.

Metabolic and Endocrine Effects: Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Discontinue thiazides before taking parathyroid function test.

Thiazide diuretic therapy may increase cholesterol and triglyceride levels.

Thiazides have been reported to increase the urinary excretion of magnesium. This may result in hypomagnesemia.

Hyperuricemia may occur or acute gout may be precipitated in certain patients taking thiazide therapy.

Acute Myopia and Secondary Angle-closure Glaucoma: HCTZ, a sulfonamide, can cause an idiosyncratic reaction, resulting in 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 drug intake 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.

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed with losartan + HCTZ. However, dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, particularly during initiation of treatment or when the dose is increased. Patients should exercise caution when driving vehicles or operating machinery.

INTERACTIONS WITH OTHER MEDICAMENTS
Losartan potassium
Lithium: Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use.
Potassium-sparing Diuretics/Supplements/Salt Substitutes: As with other medicines that block angiotensin II or its effect, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium, or other medicines that may increase serum potassium (e.g., trimethoprim-containing products) may lead to increases in serum potassium. Concomitant use is not recommended.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs) including Selective Cyclooxygenase-2 (COX-2) Inhibitors: The antihypertensive effect of angiotensin II receptor antagonists may be reduced when coadministered with NSAIDs such as selective COX-2 inhibitors and nonselective NSAIDs.
Concurrent administration of angiotensin II receptor antagonists with NSAIDs may result in an increased risk of worsening of renal function (including possible acute renal failure) and an increase in serum potassium, particularly in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and renal function monitored after initiation of therapy and periodically thereafter.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS): Dual blockade of the RAAS with angiotensin II receptor antagonists, ACE inhibitors or aliskiren is associated with increased risk of hypotension, hyperkalemia and changes in renal function (including acute renal failure) compared with monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on losartan and other agents that affect the RAAS.
Do not coadminister losartan with aliskiren in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73 m^2). Avoid concomitant use of angiotensin II receptor antagonists and ACE inhibitors in patients with diabetic nephropathy.
Tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that may induce hypotension as an adverse effect, may increase the risk of hypotension.
Other drugs: In studies, coadministration of losartan with other drugs such as hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole, and erythromycin showed no significant drug interactions. Rifampicin and fluconazole decreased the concentrations of losartan and its active metabolite.

Hydrochlorothiazide
Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension
Amantadine: Increased risk of adverse effects
Aminoglycoside antibiotics: Diuretic-induced volume depletion can potentiate aminoglycoside nephrotoxicity
Anticholinergic agents (e.g., atropine, biperidine): May increase availability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate
Antidiabetic agents (e.g., insulin, hypoglycemic agents): Dosage adjustment of the antidiabetic agent may be necessary as thiazides may impair glucose tolerance.
Diazoxide: May enhance the hyperglycemic effect of diazoxide
Antigout (e.g., probenecid, sulfinpyrazone, allopurinol): Dosage adjustment of the antigout medication may be necessary as HCTZ may raise level of serum uric acid; may increase hypersensitivity reaction with allopurinol
Calcium salts: Increased serum calcium levels due to decreased excretion
Carbamazepine: Symptomatic hyponatremia may occur. Monitor electrolytes during concomitant use.
Cardiac glycosides (e.g., digitalis): Thiazide-induced hypokalemia or hypomagnesia may favor the onset of digitalis-induced cardiac arrhythmias
Cholestyramine and colestipol resins: HCTZ absorption is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind HCTZ and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively.
Corticosteroids, ACTH, amphotericin B (parenteral), stimulant laxative, or glycyrrhizin (found in licorice): Intensified electrolyte depletion electrolyte imbalance, particularly hypokalemia
Cytotoxic agents (e.g., cyclophosphamide, methotrexate): Decreased renal excretion; increased myelosuppressive effects
Ciclosporin: May increase the risk of hyperuricemia and gout-type complications
Pressor amines (e.g., epinephrine): Possible decreased response to pressor amines but not sufficient to prevent their use
Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant
Lithium: Increased serum lithium concentrations and increased risk of lithium toxicity. Monitor serum lithium levels during concomitant use.
NSAIDs including COX-2 Inhibitors: May reduce the diuretic, natriuretic and antihypertensive effects of diuretics in some patients
Iodinated contrast media: Increased risk of acute renal failure particularly when large doses of iodinated media are used
Other antihypertensive agents: Additive effect

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: Pregnancy Category D (see **Warnings and Precautions, Fetal Toxicity**). Angiotensin II receptor antagonists should not be used during pregnancy. When pregnancy is diagnosed, immediately discontinue treatment with losartan, and, if appropriate, alternative treatment should be started.

Thiazides cross the placenta, and use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions that have occurred in adults.

Lactation: It is not known whether losartan is distributed in human milk. Thiazides appear in human milk. Discontinue breastfeeding or drug due to potential risk to breastfeeding infants, taking into consideration the importance of the drug to the mother.

Elderly: In clinical studies, there were no clinically significant differences in the efficacy and safety profiles of losartan + HCTZ in older (≥65 years) and younger (<65 years) patients.

Children: The safety and efficacy of losartan + HCTZ in pediatric patients have not been established.

UNDESIRABLE EFFECTS
The most frequently reported adverse effects with losartan include dizziness, upper respiratory infection, nasal congestion, and back pain.

Losartan potassium
Infections and infestations: Infection
Blood and lymphatic system disorders: Anemia, hemolysis, thrombocytopenia (rare)
Immune system disorders: Hypersensitivity reactions, anaphylactic reactions, angioedema (including swelling of the larynx and glottis, causing airway obstruction and or swelling of the face, lips, pharynx, and/or tongue), vasculitis including Henoch-Schönlein purpura (rare)
Endocrine disorders: Diabetic vascular disease
Metabolism and nutrition disorders: Anorexia, gout, hyperkalemia, hypoglycemia, hyponatremia, weight gain
Psychiatric disorders: Anxiety disorder, anxiety, confusion, depression, dream abnormality, insomnia, memory impairment, panic disorder, sleep disorder
Nervous system disorders: Cerebrovascular event/cerebrovascular accident (CVA), dysgeusia, headache, hypoesthesia, migraine, nervousness, paresthesia, peripheral neuropathy, somnolence, tremor
Eye disorders: Blurred vision, burning/stinging in the eye, cataract, conjunctivitis, decreased visual acquity
Ear and labyrinth disorders: Tinnitus, vertigo
Cardiac disorders: Angina pectoris, arrhythmias, atrial fibrillation, myocardial infarction, palpitation, second degree AV block, sinus bradycardia, sternalgia, syncope, tachycardia, ventricular fibrillation, ventricular tachycardia
Vascular disorders: Hypotension/orthostatic hypotension (including dose-related orthostatic effects)
Respiratory, thoracic and mediastinal disorders: Bronchitis, cough/dry cough, dyspnea, epistaxis, laryngitis, pharyngeal discomfort, pharyngitis, respiratory congestion, rhinitis, sinus disorder, sinusitis
Gastrointestinal disorders: Abdominal pain, constipation, dental pain, diarrhea, dry mouth, dyspepsia, flatulence, gastritis, nausea, obstipation, pancreatitis, vomiting
Hepatobiliary disorders: Hepatitis (rare), liver function abnormalities
Skin and subcutaneous tissue disorders: Alopecia, cellulitis, dermatitis, dry skin, ecchymosis, erythema, erythroderma, flushing, photosensitivity, pruritus, rash, sweating, urticaria
Musculoskeletal and connective tissue disorders: Arthralgia, arthritis, coxalgia, fibromyalgia, joint swelling, muscle cramps, muscle weakness, myalgia, pain (back, arm, shoulder, hip, leg, knee, musculoskeletal), rhabdomyolysis (rare), stiffness
Renal and urinary disorders: Nocturia, renal failure, renal impairment, urinary frequency, urinary tract infection
Reproductive system and breast disorders: Decreased libido, erectile dysfunction/impotence
General disorders and administration site conditions: Asthenia, chest pain, edema/swelling, facial edema, fatigue, fever, influenza-like disease, malaise
Investigations: Increases in alanine aminotransferase (ALT), BUN, serum creatinine, serum potassium, liver enzymes, and bilirubin; decreases in hemoglobin and hematocrit

Hydrochlorothiazide
Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia, bone marrow failure, granulocytopenia (rare), hemolytic anemia, leukopenia, neutropenia, thrombocytopenia
Immune system disorders: Hypersensitivity reactions, anaphylactic reactions
Endocrine disorders: Worsening of diabetic metabolic state
Metabolism and nutrition disorders: Anorexia, electrolyte imbalance, hypercalcemia, hyperglycemia, hyperuricemia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, loss of appetite
Psychiatric disorders: Insomnia
Nervous system disorders: Cephalgia, headache, lightheadedness, paresthesia, restlessness, vertigo
Eye disorders: Acute myopia and secondary angle-closure glaucoma, transient blurred vision, visual impairment, xanthopsia
Cardiac disorders: Cardiac arrhythmia
Vascular disorders: Hypotension/orthostatic hypotension
Respiratory, thoracic and mediastinal disorders: Respiratory distress (including pneumonitis and pulmonary edema)
Gastrointestinal disorders: Constipation, cramping, diarrhea, gastric irritation, gastrointestinal discomfort, nausea, pancreatitis, sialadenitis, spasms, vomiting
Hepatobiliary disorders: Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders: Alopecia, cutaneous lupus erythematosus, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, necrotizing angiitis (vasculitis and cutaneous vasculitis), photosensitivity, purpura, rash, reactivation of cutaneous lupus erythematosus, urticaria
Musculoskeletal and connective tissue disorders: Muscle cramps, muscle spasm
Renal and urinary disorders: Glycosuria, interstitial nephritis, renal dysfunction, renal failure
Reproductive system and breast disorders: Impotence
General disorders and administration site conditions: Asthenia, fever, weakness
Investigations: Increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and triglycerides

OVERDOSE AND TREATMENT

Losartan potassium
There is limited data on overdosage with losartan in humans. Losartan overdose will most likely manifest as hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

Institute symptomatic treatment and monitor vital signs if symptomatic hypotension occurs. Measures are depending on the time of drug intake and kind and severity of symptoms. Stabilization of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.

Losartan and its metabolite are not removed by hemodialysis.

Hydrochlorothiazide
The most common signs and symptoms of HCTZ overdose include electrolyte imbalance (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. Other features of overdose are lethargy, nausea and weakness. Lethargy may progress to coma within a few hours with minimal depression of respiratory and cardiovascular function without evidence of dehydration or serum electrolyte changes.

Gastrointestinal irritation and hypermotility may occur, and temporary elevation of blood urea nitrogen has been reported.

In the treatment of thiazide overdosage, gastric contents may be evacuated taking caution to avoid aspiration, particularly in unconscious patients. If the patient is conscious, induction of vomiting with ipecac syrup is effective in removing the drug from the stomach. Do not administer cathartics since they tend to promote loss of fluid and electrolytes. Treatment is generally supportive. Monitor serum electrolyte and renal function. Replacement of fluid and electrolytes may be indicated. Measures may be required to maintain respiratory, cardiovascular and renal function. Gastrointestinal irritation is usually of short duration but may be treated symptomatically.

The degree to which HCTZ is removed by hemodialysis has not been established.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632)858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Losartan potassium + Hydrochlorothiazide (Combizar®) 50 mg/ 12.5 mg Film-coated Tablet in blister pack x 10's (Box of 50's) (DRP-3753)
Losartan potassium + Hydrochlorothiazide (Combizar®) 100 mg/ 25 mg Film-coated Tablet in blister pack x 10's (Box of 50's) (DRP-3754)

Store at temperatures not exceeding 30°C.
Keep the product out of reach and sight of children.

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Trusted Quality Healthcare

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Reg. IPOPHIL
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