ZOSAAR HCT TABLETS

COMPOSITION:
Each tablet contains:

Losartan Potassium	50 mg
Hydrochlorothiazide	12.5 mg

PRODUCT DESCRIPTION:

Zosaar HCT F.C Tablet is an oval-shaped, biconvex, yellow film coated tablet; engraved with CCP on one side, with 135 on the other side.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties

Zosaar HCT (losartan potassium and hydrochlorothiazide) combines an angiotensin II receptor (type AT1) antagonist and a diuretic, hydrochlorothiazide.

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 co-administration 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.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between 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 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 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000mg)

Pharmacokinetic properties

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. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily dosing.

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.

While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times as great as that of losartan. A meal slows absorption of losartan and decreases its Cmax but has only minor effects on losartan AUC or on the AUC of the metabolite (about 10% decreased).

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. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite.

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.

During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Biliary excretion contributes to the elimination of losartan and its metabolites.

Geriatric and Gender: Losartan pharmacokinetics have been investigated in the elderly (65-75 years) and in both genders. Plasma concentrations of losartan and its active metabolite are similar in elderly and young hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolised 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.

INDICATIONS:
Hypertension: Zosaar HCT is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.

Hypertensive Patients with Left Ventricular Hypertrophy: Zosaar HCT is 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.

DOSAGE AND ADMINISTRATION:
Zosaar HCT may be administered with other antihypertensive agents.
Zosaar HCT may be administered with or without food.
Fixed-dose combination is not indicated for initial therapy.

Hypertension: The usual starting and maintenance dose of Zosaar HCT is 1 tab of Zosaar HCT 50/12.5 (losartan potassium 50 mg/hydrochlorothiazide 12.5 mg) once daily. For patients who do not respond adequately to Zosaar HCT 50/12.5, the dosage may be increased to 1 tab of losartan potassium 100 mg/hydrochlorothiazide 25 mg once daily or 2 tabs of Zosaar HCT 50/12.5 once daily. The maximum dose is 1 tab of losartan potassium 100 mg/hydrochlorothiazide 25 mg once daily or 2 tabs of Zosaar HCT 50/12.5 once daily. In general, the antihypertensive effect is attained within 3 weeks after initiation of therapy. Losartan potassium 100 mg/hydrochlorothiazide 12.5 mg is available for those patients titrated to 100 mg of Losartan who require additional blood pressure control.

Zosaar HCT should not be initiated in patients who are intravascularly volume-depleted (eg, those treated with high-dose diuretics).

Zosaar HCT is not recommended for patients with severe renal impairment (creatinine clearance ≤30 mL/min) or for patients with hepatic impairment.

No initial dosage adjustment of Zosaar HCT is necessary for elderly patients. Losartan potassium 100 mg/hydrochlorothiazide 25 mg should not be used as initial therapy in elderly patients.

Hypertensive Patients with Left Ventricular Hypertrophy: The usual starting dose is losartan 50 mg once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg) and, if needed, the dose should then be increased to losartan 100 mg and hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg and hydrochlorothiazide 25 mg once daily. Zosaar HCT 50/12.5, Losartan potassium 100 mg/hydrochlorothiazide 12.5 mg and losartan potassium 100 mg/hydrochlorothiazide 25 mg are suitable alternative formulations in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

CONTRAINDICATIONS:
Zosaar HCT 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.

WARNINGS
Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, Zosaar HCT should be discontinued as soon as possible.
The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.
These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.
Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of Zosaar HCT as soon as possible.
Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohydramnios is observed, Zosaar HCT should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories 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 means of reversing hypotension and/or substituting for disordered renal function.
Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Acute Respiratory Toxicity
Hydrochlorothiazide
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Zosaar HCT should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Hypotension — Volume-Depleted Patients
In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with Zosaar HCT. This condition should be corrected prior to administration of Zosaar HCT.

Impaired Hepatic Function
Losartan Potassium and Hydrochlorothiazide
Zosaar HCT is not recommended for patients with hepatic impairment who require titration with losartan. The lower starting dose of losartan recommended for use in patients with hepatic impairment cannot be given using Zosaar HCT.
Hydrochlorothiazide
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Hypersensitivity Reaction
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.
Systemic Lupus Erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
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.
Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.
Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

PRECAUTIONS:
General
Hypersensitivity: Angioedema.
Losartan Potassium and Hydrochlorothiazide
In patients treated with various doses of losartan and hydrochlorothiazide, there is a potential dose-related decrease in the hypokalemic response to hydrochlorothiazide as the dose of losartan was ncreased, as well as a dose-related decrease in serum uric acid with increasing doses of losartan.
Hydrochlorothiazide
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe 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 circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is lifethreatening. In actual salt depletion, appropriate replacement is the therapy of choice.

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

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Renal Function
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with losartan; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with losartan.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Symptomatic Hypotension: A patient receiving Zosaar HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Zosaar HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving Zosaar HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician

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

Nursing Mothers
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.

Pediatric Use
Safety and effectiveness of Zosaar HCT in pediatric patients have not been established.

DRUG INTERACTIONS:

Losartan Potassium

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Lithium: As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

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

Dual blockade of the renin-angiotensin-aldosterone system: Dual blockade of the renin-angiotensinaldosterone system is associated with increased risk of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure). Closely monitor blood pressure, renal function, and electrolytes in patients on Zosaar HCT and ACE inhibitors.

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)** — dosage adjustment of the antidiabetic drug may be required.
- **Other antihypertensive drugs** — additive effect or potentiation.
- **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.
- **Corticosteroids, ACTH, or glycyrrhizin (found in liquorice)** — intensified electrolyte depletion, particularly hypokalemia.
- **Pressor amines (e.g., norepinephrine)** — possible decreased response to pressor amines but not sufficient to preclude their use.
- **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased responsiveness to the muscle relaxant.
- **Lithium** — should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
- **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors(COX-2 Inhibitors)** — The administration of a non-steroidal anti-inflammatory agent, including a selective cyclooxygenase-2 inhibitor, can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when Zosaar HCT and non-steroidal anti-inflammatory agents, including selective cyclooxygenase-2 inhibitors, are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

In patients receiving diuretic therapy, co-administration 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.

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

The following adverse events have been reported: asthenia/fatigue, diarrhea, nausea, headache, bronchitis, pharyngitis.

Adverse events were somewhat more frequent in the elderly compared to non-elderly patients.

Superficial peeling of palms and hemolysis were reported in one subject treated with losartan potassium

With regards to losartan, other adverse experiences that have been reported with losartan, are listed below:

- ***Body as a whole:*** chest pain, facial edema, fever, orthostatic effects, syncope.
- ***Cardiovascular:*** angina pectoris, arrhythmias including atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia and ventricular fibrillation, CVA, hypotension, myocardial infarction, second degree AV block.
- ***Digestive:*** anorexia, constipation, dental pain, dry mouth, dyspepsia, flatulence, gastritis, vomiting.
- ***General disorders and administration site conditions:*** malaise
- ***Hematologic:*** anemia
- ***Metabolic:*** gout
- ***Musculoskeletal:*** arm pain, arthralgia, arthritis, fibromyalgia, hip pain, joint swelling, knee pain, leg pain, muscle cramps, muscle weakness, musculoskeletal pain, myalgia, shoulder pain, stiffness
- ***Nervous System/Psychiatric:*** anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, insomnia, libido decreased, memory impairment, migraine, nervousness, panic disorder, paresthesia, peripheral neuropathy, sleep disorder, somnolence, tremor, vertigo
- ***Respiratory:*** dyspnea, epistaxis, nasal congestion, pharyngeal discomfort, respiratory congestion, rhinitis, sinus disorder;
- ***Skin:*** alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, sweating, urticaria
- ***Special Senses:*** blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity, taste perversion, tinnitus
- ***Urogenital:*** impotence, nocturia, urinary frequency, urinary tract infection.

With Hydrochlorothiazide, adverse experiences that have been reported with hydrochlorothiazide, are listed below:

- ***Body as a whole:*** weakness
- ***Digestive:*** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation
- ***Hematologic:*** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia
- ***Hypersensitivity:*** purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema
- ***Metabolic:*** hyperglycemia, glycosuria, hyperuricemia
- ***Musculoskeletal:*** muscle spasm
- ***Nervous System/Psychiatric:*** restlessness
- ***Renal:*** renal failure, renal dysfunction, interstitial nephritis
- ***Skin:*** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis
- ***Special Senses:*** transient blurred vision, xanthopsia.
- ***Eye disorders:*** Frequency 'not known': Choroidal effusion, acute myopia, acute angle-closure glaucoma

Neoplasm benign, malignant and unspecified (incl cysts and polyps)
Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Respiratory, thoracic and mediastinal disorders
Frequency 'very rare': Acute respiratory distress syndrome (ARDS)

Description of selected adverse reactions
Non-melanoma skin cancer. Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

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

OVERDOSAGE:
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/m^2 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.

STORAGE:
Store below 30°C. Protect from light and moisture.
Keep out of reach of children.

PACKING:
30 tables, 10 tablets in an Aluminium/PVC blister, 3 blisters packed in an aluminum bag, and 1 Aluminium bag packed in the box.

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Malaysia Registration No. MAL16045051ACZ

Revision date: July 2024

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105.07.28 製
105.10.21 修改內容
107.12.05 輸出生產
108.10.16 修改內容&版號B
108.10.21 修改內容
108.10.25 修改內容
109.02.18 修改內容&版號C
109.02.24 修改內容&版號B
110.04.09 輸出生產
111.04.18 修改內容&版號C
111.07.19 修改內容
111.07.26 修改內容
112.01.13 修改內容&版號D
112.01.31 修改內容&版號C
112.02.03 輸出生產
113.04.29 修改內容(Packing)&版號D
113.05.02 修改內容(Revision date)
113.05.28 修改內容
113.07.26 修改內容

210x650mm 正反印刷 210x650mm