PRODUCT CIRCULAR S-THL-OG0954A-T-032022

RCN100001302-TH

Tablets

FORTZAAR®

(losartan potassium and hydrochlorothiazide)

THERAPEUTIC CLASS

FORTZAAR (losartan potassium and hydrochlorothiazide) is the first combination of an angiotensin II receptor (type AT_1) antagonist and a diuretic.

INDICATIONS

Hypertension

FORTZAAR is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

FORTZAAR is a combination of losartan (COZAAR) and hydrochlorothiazide. In patients with hypertension and left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, reduces the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy (see RACE).

DOSAGE AND ADMINISTRATION

FORTZAAR may be administered with other antihypertensive agents.

FORTZAAR may be administered with or without food.

Hypertension

The usual starting and maintenance dose of HYZAAR is one tablet of HYZAAR 50/12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. For patients who do not respond adequately to HYZAAR 50/12.5, the dosage may be increased to one tablet of FORTZAAR (losartan 100 mg/hydrochlorothiazide 25 mg) once daily or two tablets of HYZAAR 50/12.5 once daily. The maximum dose is one tablet of FORTZAAR once daily or two tablets of HYZAAR 50/12.5 once daily. In general, the antihypertensive effect is attained within three weeks after initiation of therapy. HYZAAR 100/12.5 (losartan

100 mg/hydrochlorothiazide 12.5 mg) is available for those patients titrated to 100 mg of COZAAR who require additional blood pressure control.

FORTZAAR should not be initiated in patients who are intravascularly volume-depleted (e.g., those treated with high-dose diuretics).

FORTZAAR 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 HYZAAR 50/12.5 is necessary for elderly patients. FORTZAAR should not be used as initial therapy in elderly patients.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of losartan 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. HYZAAR 50/12.5, HYZAAR 100/12.5 and FORTZAAR 100/25 are suitable alternative formulations in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

CONTRAINDICATIONS

FORTZAAR is contraindicated in:

- patients who are hypersensitive to any component of this product.
- patients with anuria.
- patients who are hypersensitive to other sulfonamide-derived drugs.
- pregnant woman

FORTZAAR should not be administered with aliskiren in patients with diabetes (see DRUG INTERACTIONS).

PRECAUTIONS

Losartan-Hydrochlorothiazide

Fetal Toxicity

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 FORTZAAR as soon as possible. See PREGNANCY.

Hypersensitivity: Angioedema. See SIDE EFFECTS.

Hepatic and Renal Impairment

FORTZAAR is not recommended for patients with hepatic impairment or severe renal impairment (creatinine clearance ≤30 mL/min) (see DOSAGE AND ADMINISTRATION).

Losartan

Renal Function Impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of therapy.

Other drugs that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with renovascular disease such as bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Similar effects have been reported with losartan; these changes in renal function may be reversible upon discontinuation of therapy.

Increases in Serum Potassium

Concomitant use of other drugs that may increase serum potassium may lead to hyperkalemia (see DRUG INTERACTIONS).

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during

intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see DRUG INTERACTIONS).

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. 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.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]) with increasing cumulative dose of hydrochlorothiazide has been observed in epidemiological studies. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for non-melanoma skin cancer.

Patients taking hydrochlorothiazide should be informed of the risk of non-melanoma skin cancer and advised to take preventive measures to reduce sun and artificial UVA exposure. Patients should regularly check their skin for new lesions and promptly report suspicious skin lesions to their physicians for

evaluation. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous non-melanoma skin cancer. (See also SIDE EFFECTS.)

Acute respiratory distress

Very rare severe cases of acute respiratory distress including pneumonitis and pulmonary edema have been reported after taking hydrochlorothiazide. FORTZAAR should be discontinued, and appropriate treatment should be given if the patient presents with acute respiratory distress. (See SIDE EFFECTS.)

Other

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

PREGNANCY

FORTZAAR is contraindicated in pregnant women.

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

Although there is no experience with the use of FORTZAAR in pregnant women, animal studies with losartan potassium have demonstrated fetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, fetal renal perfusion, which is dependent upon the development of the renin angiotensin system, begins in the second trimester; thus, risk to the fetus increases if FORTZAAR is administered during the second or third trimesters of pregnancy.

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 FORTZAAR as soon as possible.

These adverse outcomes are usually associated with the 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

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 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 FORTZAAR, unless it is considered life-saving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. 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 FORTZAAR for hypotension, oliguria, and hyperkalemia.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

NURSING MOTHERS

It is not known whether losartan is excreted in human 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 in children have not been established.

Neonates with a history of *in utero* exposure to FORTZAAR:
If oliguria or hypotension occur, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

USE IN THE ELDERLY

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

RACE

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study, the benefits of losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered

blood pressure in Black patients. In the overall LIFE study population (n=9193), treatment with losartan resulted in a 13.0% risk reduction (p=0.021) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this study, losartan decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n=8660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction (p=0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan (p=0.03). 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%, 25.9 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1000 patient-years) on losartan.

DRUG INTERACTIONS

Losartan

In clinical pharmacokinetic trials, no drug interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see Hydrochlorothiazide*, Alcohol, barbiturates, or narcotics* below), ketoconazole and erythromycin. Rifampin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

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

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.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor

antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) 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. Closely monitor blood pressure, renal function, and electrolytes in patients on FORTZAAR and other agents that affect the RAAS. Do not co-administer aliskiren with FORTZAAR in patients with diabetes. Avoid use of aliskiren with FORTZAAR in patients with renal impairment (GFR <60 mL/min).

Grapefruit juice contains components that inhibit CYP 450 enzymes and may lower the concentration of the active metabolite of losartan which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking FORTZAAR.

Hydrochlorothiazide

When given 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.

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., adrenaline) - 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 - Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended. Refer to the package inserts for lithium preparations before use of such preparations.

Non-Steroidal Anti-inflammatory Drugs Including Cyclooxygenase-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 diuretics.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Drug/Laboratory Test Interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see PRECAUTIONS).

SIDE EFFECTS

In clinical trials with losartan potassium-hydrochlorothiazide, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse

experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo.

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

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

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

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

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

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

Immune system disorders: Anaphylactic reactions, angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue has been

reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors.

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

Psychiatric disorders: Insomnia, restlessness.

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

Eye disorders: Xanthopsia, transient blurred vision.

Cardiac disorders: Palpitation, tachycardia.

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

Respiratory, thoracic and mediastinal disorders: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress, pneumonitis and pulmonary edema. Acute respiratory distress has been reported in very rare instances (see PRECAUTIONS).

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

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

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

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

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

Reproductive system and breast disorders: Erectile dysfunction/impotence.

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

Investigations: Liver function abnormalities.

Description of Selected Side Effects

Non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)

Based on available data from epidemiological studies, a cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer (BCC and SCC) has been observed.

The largest 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 cumulative hydrochlorothiazide use (≥50,000 mg) was associated with an adjusted odds ratio (OR) of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A cumulative dose-response relationship was observed for both

BCC and SCC. Another study evaluated the association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip cancer were matched with 63,067 population controls. A cumulative dose-response relationship was demonstrated with an adjusted OR of 2.1 (95% CI: 1.7-2.6) for ever-use, increasing to an OR of 3.9 (95% CI: 3.0-4.9) for high use (≥25,000 mg) and an OR of 7.7 (95% CI: 5.7-10.5) for the highest cumulative dose (≥100,000 mg).

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan-hydrochlorothiazide. Hyperkalemia (serum potassium >5.5 mEq/L) occurred in 0.7% of patients, but in these trials, discontinuation of losartan-hydrochlorothiazide due to hyperkalemia was not necessary. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

OVERDOSAGE

No specific information is available on the treatment of overdosage with FORTZAAR. Treatment is symptomatic and supportive. Therapy with FORTZAAR should be discontinued and the patient observed

closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan

Limited data are available in regard to 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 the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

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.

AVAILABILITY

FORTZAAR tablets, each containing 100 mg losartan potassium and 25 mg hydrochlorothiazide, are supplied in pack of 30's.

Storage

Store at room temperature (15-30℃).

Warning

1. This drug is prohibited in pregnant woman.
2. Consult physician if lethargy, or nausea, vomiting occur.
3. If angioedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and or tongue occurs, discontinue the drug and consult physician immediately.
4. Impairment of renal function may occur, so use with caution.
5. Development of hyperkalemia may occur, concomitant use of potassium supplement or potassium sparing diuretic is not recommended.

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