PRODUCT CIRCULAR

PAK-FTZ-T-082009

Tablets
FORTZAAR®†
(losartan potassium and hydrochlorothiazide)

I. THERAPEUTIC CLASS

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

II. 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).

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

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

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

FORTZAAR 100-25 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 and HYZAAR 100/25 are suitable alternative formulations in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

IV. 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.

V. PRECAUTIONS

Losartan-Hydrochlorothiazide

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 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.

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.

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.

VI. PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, FORTZAAR should be discontinued 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.

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.

VII. NURSING MOTHER

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.

VIII. PEDIATRIC USE

Safety and effectiveness in children have not been established**.**

IX. USE IN THE ELDERLY

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

X. 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.

XI. 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, or salt substitutes containing potassium 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.

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 - 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).

XII. 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:

Blood and lymphatic system: Thrombocytopenia
Hypersensitivity: 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. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely with losartan.

Gastrointestinal: Hepatitis has been reported rarely in patients treated with losartan, diarrhea.

Respiratory: Cough has been reported with losartan.

Skin: Urticaria, erythroderma has been reported with losartan. Photosensitivity has been reported with losartan potassium-hydrochlorothiazide.

XIIa. Laboratory Test Findings

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

XIII. 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.

XIV. AVAILABILITY

FORTZAAR® PAK-FTZ-T-082009
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FORTZAAR Tablets are supplied in blister package of 14 tablets (1X 14’s strip). Each film coated tablet contains 100mg losartan potassium and 25 mg hydrochlorothiazide U.S.P.