LOCAL PRODUCT CIRCULAR **LPC-OG0954A-T-102024-Malaysia**

Tablets
HYZAAR/FORTZAAR®
(losartan potassium and hydrochlorothiazide)

I. THERAPEUTIC CLASS

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

II. INDICATIONS

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

Hypertensive Patients With Left Ventricular Hypertrophy
HYZAAR/FORTZAAR 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. (See PRECAUTIONS, *Race,* CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects, Losartan Potassium, Reduction in the Risk of Stroke, Race* and DOSAGE AND ADMINISTRATION.)

III. CLINICAL PHARMACOLOGY

Mechanism of Action

Losartan-Hydrochlorothiazide

The components of HYZAAR/FORTZAAR have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

Pharmacokinetics

Absorption

Losartan
Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardized meal.

Distribution

Losartan
Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Metabolism

Losartan
About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Losartan
Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the feces. Following an intravenous

dose of ^{14}C-labeled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the feces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized 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.

Characteristics in Patients

Losartan-Hydrochlorothiazide

The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

Losartan

The plasma concentrations of losartan and its active metabolite in elderly hypertensives are not significantly different from those in young hypertensives.

Plasma concentrations of losartan were up to 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females. This apparent pharmacokinetic difference is not judged to be of clinical significance.

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1.7-fold greater than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 mL/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in hemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor the active metabolite can be removed by hemodialysis.

Pharmacodynamics

Losartan

Losartan inhibits systolic and diastolic pressor responses to angiotensin II infusions. At peak, 100 mg of losartan potassium inhibits these responses by approximately 85%; 24 hours after single and multiple-dose administration, inhibition is about 26-39%.

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. During chronic (6 weeks) treatment of hypertensive patients with 100 mg/day losartan, approximately 2-3 fold increases of plasma angiotensin II were observed at time of peak plasma drug concentrations. In some patients, greater increases were observed, particularly during short term (2 weeks) treatment. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent at 2 and 6 weeks, indicating effective angiotensin II

receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin II levels declined to untreated levels within 3 days. Effects of HYZAAR/FORTZAAR on PRA and angiotensin II levels were similar to those observed with 50 mg of losartan.

Since losartan is a specific antagonist of the angiotensin II receptor type AT_1, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. In a study which compared the effects of 20 mg and 100 mg of losartan potassium and an ACE inhibitor on responses to angiotensin I, angiotensin II and bradykinin, losartan was shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin. This finding is consistent with losartan's specific mechanism of action. In contrast, the ACE inhibitor was shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

Plasma concentrations of losartan and its active metabolite and the antihypertensive effect of losartan increase with increasing dose. Since losartan and its active metabolite are both angiotensin II receptor antagonists, they both contribute to the antihypertensive effect.

In a single-dose study in normal males, the administration of 100 mg of losartan potassium, under dietary high- and low-salt conditions, did not alter glomerular filtration rate, effective renal plasma flow or filtration fraction. Losartan had a natriuretic effect which was more pronounced on a low-salt diet and did not appear to be related to inhibition of early proximal reabsorption of sodium. Losartan also caused a transient increase in urinary uric acid excretion.

In nondiabetic hypertensive patients with proteinuria (≥2 g/24 hours) treated for 8 weeks, the administration of losartan potassium 50 mg titrated to 100 mg significantly reduced proteinuria by 42%. Fractional excretion of albumin and IgG also was significantly reduced. In these patients, losartan maintained glomerular filtration rate and reduced filtration fraction.

In postmenopausal hypertensive women treated for 4 weeks, 50 mg of losartan potassium had no effect on renal or systemic prostaglandin levels.

Losartan has no effect on autonomic reflexes and no sustained effect on plasma norepinephrine.

Losartan potassium, administered in doses of up to 150 mg once daily, did not cause clinically important changes in fasting triglycerides, total cholesterol or HDL-cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

Generally losartan caused a decrease in serum uric acid (usually <0.4 mg/dL) which was persistent with chronic therapy. In controlled clinical trials in hypertensive patients, no patients were discontinued due to increases in serum creatinine or serum potassium.

In a 12-week, parallel-design study in patients with left ventricular failure (New York Heart Association Functional Classes II-IV), most of whom were receiving diuretics and/or

digitalis, losartan potassium administered in once-daily doses of 2.5, 10, 25 and 50 mg was compared to placebo. The 25-mg and 50-mg doses produced positive hemodynamic and neurohormonal effects which were maintained for the length of the study. Hemodynamic responses were characterized by an increase in cardiac index and decreases in: pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate. The occurrence of hypotension was dose related in these heart failure patients. Neurohormonal results were characterized by a reduction in circulating levels of aldosterone and norepinephrine.

IV. DOSAGE AND ADMINISTRATION

HYZAAR/FORTZAAR may be administered with other antihypertensive agents. HYZAAR/FORTZAAR may be administered with or without food.

Fixed dose combination is not indicated for initial therapy.

Hypertension

The usual starting and maintenance dose of HYZAAR/FORTZAAR is one tablet of HYZAAR 50-12.5 (losartan potassium 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 potassium 100mg/hydrochlorothiazide 25mg) 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 potassium 100 mg/hydrochlorothiazide 12.5 mg) is available for those patients titrated to 100 mg of COZAAR who require additional blood pressure control.

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

HYZAAR/FORTZAAR is not recommended for patients with severe renal impairment (creatinineclearance $\leq$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.

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 are suitable alternative formulations in patientswho would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

V. CONTRAINDICATIONS

HYZAAR/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.

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

VI. 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 HYZAAR/FORTZAAR as soon as possible. See PREGNANCY.

Hypersensitivity: Angioedema See SIDE EFFECTS.

Hepatic and Renal Impairment
HYZAAR/FORTZAAR is not recommended for patients with hepatic impairment or severe renalimpairment (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.

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 (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.

Acute respiratory toxicity
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, HYZAAR/FORTZAAR should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.(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.

VII. PREGNANCY

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

Although there is no experience with the use of HYZAAR/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 HYZAAR/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 HYZAAR/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 HYZAAR/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 HYZAAR/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.

VIII. 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.

IX. PEDIATRIC USE

Safety and effectiveness in children have not been established.

Neonates with a history of *in utero* exposure to HYZAAR/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.

X. 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).

XI. 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% ofthe 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%, 41.8per 1000 patient-years) on losartan.

XII. 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 consequencesof 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 HYZAAR/FORTZAAR and other agents that affect the RAAS. Do not co-administer aliskiren with HYZAAR/FORTZAAR in patients with diabetes. Avoid use of aliskiren with HYZAAR/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 HYZAAR.

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-2inhibitor 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).

XIII. 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 HYZAAR/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. Intestinal angioedema has been reported in patients treated with angiotensin II receptors antagonists including few cases with losartan.

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. Frequency 'not known': Choroidal effusion, acute myopia, acute angle-closure glaucoma

*Cardiac disorder*s: 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. Frequency 'very rare': Acute respiratory distress syndrome (ARDS) (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 (NMSC):

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide (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 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 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 (95% CI: 3.0-4.9) for high use (~ 25,000 mg) and OR 7.7 (95% CI: 5.7-10.5) for the highest cumulative dose (~ 100,000 mg).

XIIIa. 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.

XIV. OVERDOSAGE

No specific information is available on the treatment of overdosage with HYZAAR/FORTZAAR. Treatment is symptomatic and supportive. Therapy with HYZAAR/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.

XV. APPEARANCE & AVAILABILITY

HYZAAR 50-12.5 (losartan potassium 50mg/hydrochlorothiazide 12.5mg): Yellow oval shaped film-coated tablet. One side plain, the other side imprinted 717.
HYZAAR 50-12.5 is available in blister packs of 30's/box.

HYZAAR 100-12.5 (losartan potassium 100mg/hydrochlorothiazide 12.5mg): White to off-white, oval, film-coated tablet with '745' debossed on one side and plain on the other.
HYZAAR 100-12.5 is available in blister packs of 30's/box.

FORTZAAR (losartan potassium 100mg/hydrochlorothiazide 25mg): A light yellow, oval shaped, film-coated tablet with '747' on one side and plain on the other.
FORTZAAR is available in blister packs of 30's/box.

XVI. SHELF LIFE

Please refer to the expiry date on the outer carton.

XVII. STORAGE CONDITION

Store below 30°C, protect from light.

XVIII. MANUFACTURER

Organon Pharma (UK)
Limited Shotton Lane,
Cramlington,
Northumberland, NE23
3JU, United Kingdom.

XIX. PRODUCT REGISTRATION HOLDER

Organon Malaysia Sdn. Bhd.
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50490 Kuala Lumpur, Malaysia.

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