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FORTZAAR

Merck Sharp & Dhome

1. NAME OF THE MEDICINAL PRODUCT

FORTZAAR 100/25

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FORTZAAR contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide.

3. PHARMACEUTICAL FORM

Coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with essential hypertension who have responded insufficiently to treatment with an AII receptor antagonist or a diuretic as monotherapy.

4.2 Posology and method of administration

FORTZAAR can be taken before, during and after meals.

The usual starting and maintenance dose is one tablet HYZAAR (kaliumlosartan/hydrochlorothiazide 50/12.5) once daily. If necessary, the dosage may be increased to one tablet FORTZAAR daily. If patients will be treated with kaliumlosartan/hydrochlorothiazide following monotherapy with a diuretic, the diuretic therapy should be stopped 2-3 days before kaliumlosartan/hydrochlorothiazide is started.

No initial dosage adjustment is necessary for elderly patients.

4.3 Contra-indications

FORTZAAR is contraindicated in:

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

4.4 Special warnings and special precautions for use

Losartan

Hypersensitivity: Angioedema. See Side Effects

Symptomatic Hypotension

FORTZAAR should not be initiated in patients who are intravascularly volume-depleted because symptomatic hypotension may occur. Such situations are most likely in patients who are being treated with high-dose diuretics, are on a low-sodium diet or are experiencing vomiting or diarrhea. In patients with concurrent heart insufficiency there may be an increased risk of symptomatic hypotension. This is true in particular for severe forms of heart insufficiency as may be manifest from the concomitant use of high-dose diuretics, hyponatremia or renal impairment. In such patients, treatment should preferably be initiated in the hospital. In general, intravascular volume depletion should be corrected prior to administration of 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 the 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.

Hemodialysis patients

Pharmacokinetic data indicate that the plasma concentration of losartan is highly variable in this patient group, and on average is significantly higher than in other patients.

Hepatic Disease

Based on pharmacokinetic data significantly increased plasma concentrations of losartan in cirrhotic patients are demonstrated,

Operation/narcosis

In patients undergoing major surgery, or during nar-

cosis with agents causing hypotension, losartan blocks the action of angiotensin II after compensatory renin secretion. If hypotension occurs, which may be attributed to this mechanism, it may be corrected by volume replenishment.

Hydrochlorothiazide

Hypotension and Electrolyte/Fluid Imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated hypertensive patients but is more likely in the presence of fluid or electrolyte imbalance. Periodic determination of serum electrolytes should be performed at appropriate intervals as in any patient receiving diuretics.

Renal Function Impairment

Thiazides are not appropriate diuretics for use in patients with renal impairment, and are ineffective at creatinine clearance values of 30 ml/min or below (i.e., moderate or severe renal insufficiency).

Hepatic Disease

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.

Metabolic and Endocrine Effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see 'Interaction with other medicaments and other forms of interaction').

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 produces a slight decrease in uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia to some degree.

Other precautions

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.

FORTZAAR

Pediatric Use

FORTZAAR has not been studied in children.

4.5 Interaction with other medicaments and other forms of interaction

Losartan

Other hypertensives

Concurrent use with other antihypertensives may potentiate the antihypertensive effect.

Lithium

Although no specific research has been performed, losartan may reduce lithium excretion. That is why serum lithium levels should be carefully monitored when administering lithium salts.

Other drugs

Losartan is converted into the active carboxyl acid metabolite primarily by cytochrome P450 (CYP) 2C9. Repeated administration of fluconazole, a CYP2C9 inhibitor caused approximately 50% reduction in active metabolite AUC in an interaction study with healthy volunteers. The clinical consequence of this is as yet unknown. Concomitant administration of fluvastatine, a mild CYP2C9 inhibitor, caused no clinically relevant interaction.

Other interaction studies show that the cytochrome P450-3A4 inhibitors ketoconazole, itraconazole and erythromycine do not affect the metabolism of losartan.

Phenobarbital, a metabolism enzyme inducer, has no clinically relevant influence on losartan metabolism. However, concomitant administration of inducer rifampin achieved a 40% reduction in the plasma concentration of the active metabolite. The clinical relevance of this is as yet unknown.

No clinically relevant drug interactions have been found with hydrochlorothiazide, digoxine, warfarine and cimetidine in clinical pharmacokinetic trials.

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.

The antihypertensive effect of losartan may be attenuated by non-steroidal anti-inflammatory drugs (NSAID's).

Hydrochlorothiazide

When given concurrently with the following drugs, interactions may occur:

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 may occur.

Pressor Amines (e.g., Epinephrine)

Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal Muscle Relaxants, Nondepolarizing

Possible increased responsiveness to tubocurarine.

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.

Prostaglandin Synthetase Inhibitors

In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

Drug/Laboratory Test Interactions

Although no specific research has been performed, it is to be expected that serum potassium could increase with concomitant use of potassium supplements and salt substitutes containing potassium, particularly in patients with renal impairment.

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see 'Special warnings and special precautions for use').

4.6 Pregnancy and lactation

Use during Pregnancy

There are insufficient data on the use of FORTZAAR during pregnancy in man to evaluate potential harmfulness. In animal experiments losartan proved to be harmful. When losartan was administered to rats during late gestation or during lactation, it produced renal abnormalities, reduced body weight and increased mortality in offspring.

On the basis of the pharmacologic action of losartan, harmfulness due to use in pregnancy is possible. The mechanism of this is believed to be pharmacologically mediated through the effects of the renin-angiotensin system.

Fetal and neonatal morbidity and mortality can be caused by ACE inhibitors when administered to pregnant women during the second and third trimesters of pregnancy. Use of drugs that directly act on the renin-angiotensin system during this period have been associated with fetal and neonatal disorders, including hypotension, renal insufficiency, hyperkalemia and/or skull hypoplasia. As a result of reduced renal function, oligohydramnios may occur in the fetus. This may lead to limb contractures, cranio-

facial deformations and hypoplastic lung development. While no data are available, this could also occur with angiotensin II receptor antagonists.

The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

From clinical observations it has appeared that thiazides may be harmful to the fetus. Thiazides cross the placental barrier and appear in the cord blood. The possible hazards to the fetus include fetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult.

If children are desired and in case of pregnancy, FORTZAAR should be discontinued as soon as possible. Furthermore, patient should immediately contact the treating physician in order to decide on an alternative treatment. It would be wise to point this out to the patient at the start of treatment.

Use during Lactation

Thiazides appear in human milk. It is not known whether losartan is excreted in human milk. However, significant levels of losartan and the active metabolite were shown to be present in rat 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.

4.7 Effects on ability to drive and use machines

There are no known data on the effect on the ability to drive. In view of the possible occurrence of the side effect dizziness, one should take a negative effect on the ability to drive and operate machines into account.

4.8 Undesirable effects

The side effects reported in the combined use of losartan potassium and hydrochlorothiazide are generally mild and transient and do not give rise to discontinuation of treatment. The occurrence of dizziness, headache and asthenia/fatigue are the main side-effects in the use of kaliumlosartan/hydrochlorothiazide. Also the side-effects of the separate ingredients should be taken into account; these include palpitation, nausea, rash, sweating, myalgia, abdominal pain, migraine, anemia, and liver function abnormalities.

The following adverse reactions have been reported in post-marketing experience:

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 purpera, has been reported rarely with losartan.

Allergic skin reactions: pruritis, rash, urticaria have been reported with losartan.

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

Respiratory: Cough has been reported with losartan.

Laboratory Test Findings

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

4.9 Overdose

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 and/or gastric lavage if ingestion is recent, and correction of dehydration, electrolyte imbalance 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. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Losartan - Potassium
The components 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. As a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, aldosterone secretion, and the levels of angiotensin II and decreases serum potassium, while losartan blocks all physiologically relevant effects of angiotensin II, including inhibition of aldosterone secretion; this could attenuate the potassium loss associated with the use of hydrochlorothiazide.

Generally losartan causes a slight decrease in serum uric acid which is persistent in chronic therapy. Hydrochlorothiazide has been shown to cause modest increases in uric acid. When the combination was used, an elevation of uric acid was observed, although somewhat less frequently than with hydrochlorothiazide alone.

The antihypertensive effect of losartan/hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of losartan/hydrochlorothiazide had no clinically significant effect on heart rate.

A study in patients with severe hypertension showed the utility of kaliumlosartan/hydrochlorothiazide administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

FORTZAAR is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥65 years) patients and is not only effective in mild but also severe hypertension.

Losartan
Losartan belongs to a new class of antihypertensives and is an effective, synthetic, orally active angiotensin II receptor antagonist. Angiotensin II, a potent vasoconstrictor, is the active hormone of the renin-angiotensin system and a major determinant in the pathophysiology of hypertension. Angiotensin II also stimulates smooth muscle cell proliferation. Angiotensin II binds to the AT1 receptor found in many tissues (e.g., vascular smooth muscles, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. AT2 receptors are not blocked by losartan.

Both losartan and the pharmacologically active metabolite bind selectively to the AT1 receptor. Losartan and its active metabolite have no agonist effects. Losartan does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Losartan differs from ACE inhibitors in that it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin.

In a study specifically designed to assess the incidence of cough in patients treated with losartan as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients treated with the ACE inhibitor lisinopril. In comparative research,

there was no evidence of the occurrence of cough in patients given losartan.

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

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and an antihypertensive. The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure. The diuretic action affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

5.2 Pharmacokinetic properties

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 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. The effect of food on the plasma concentration profile of losartan in this formulation has not been established.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma half-life of hydrochlorothiazide is 5.6-14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours.

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. Hydrochlorothiazide is excreted in human milk.

Biotransformation

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 primarily is attributed to losartan and its active metabolite. The conversion of losartan into the active metabolite is primarily catalyzed by the enzyme cytochrome P450 2C9. 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.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized.

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.

The terminal half-life of losartan and the active metabolite is about 2 hours and 6-9 hours, respectively. During once-daily dosing, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretions 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.

Hydrochlorothiazide
Hydrochlorothiazide is eliminated rapidly by the kidney. 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
The plasma concentrations of losartan and its active metabolite in elderly hypertensives are not statistically significantly different from those in young hypertensives. The plasma concentrations of losartan in hypertensive patients are statistically significantly higher in women in comparison with men. Concentrations of the active metabolite are similar in men and women.

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.

Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide
The plasma concentrations of hydrochlorothiazide in hypertensive patients with reduced renal function are statistically significant higher in comparison to patients with normal renal function.

5.3 Preclinical safety data
In animal experiments, losartan had a negative effect on late-fetal development (see 'Use during pregnancy and lactation'). Otherwise there are no specific data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Each tablet contains the following inactive ingredients: microcrystalline cellulose (E 460a), lactose hydrous, pregelatinized mais starch, magnesium stearate (E 572), hydroxypropyl cellulose (E 463), hydroxypropyl methylcellulose (E 464), titanium dioxide (E 171), quinoline yellow (E 104) and carnauba wax (E 903).
FORTZAAR also contains 8.48 mg (0.216 mEq) of potassium.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years, the expiry date is printed on the package after "Not to be used after" and on the blister strips after "exp", followed by month and year.

6.4 Special precautions for storage
Do not store above 30° C. Store in the closed original package.

6.5 Nature and contents of container
Box with three 10-tablet PVC/PE/PVC/Al coated blister strips and box with five 10-tablet PVC/PE/PVDC coated blister strip.

6.6 Instructions for use/handling
Not applicable.

6.7 Name of style and permanent address or registered place of business of the holder of the marketing authorization
Merck Sharp & Dohme BV, P.O Box 581, 2003 PC Haarlem

7. MARKETING AUTHORIZATION NUMBER
Entered in the register under RVG 23597

8. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION
11 July 2003

Here above is the latest Summary of Products Characteristics submitted to the Ministry of Health: Kuwait Sep 05, UAE Sep 05, Bahrain Sep 05