SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

FORTZAAR™ Tablet

COMPOSITION

Each FORTZAAR Tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.

FORTZAAR contains 8, 48 mg (0,216 mEq) of potassium.

FORTZAAR contains lactose

In addition, FORTZAAR contain the following inactive ingredients:

Quinoline yellow aluminium lake; carnauba wax; hydroxypropyl cellulose; hypromellose; lactose hydrous; magnesium stearate; microcrystalline cellulose; pregelatinised starch; titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3. Other hypotensives

PHARMACOLOGICAL ACTION

Losartan potassium is an angiotensin II receptor (type AT_1) antagonist and hydrochlorothiazide is a diuretic.

LOSARTAN

Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system, and a major determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan is a synthetic, orally active compound which binds selectively to the AT_1 receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block the actions of angiotensin II, regardless of the source of synthesis.

HYDROCHLOROTHIAZIDE

The mechanism of the antihypertensive effect of thiazides is unknown.

Hydrochlorothiazide, when used as a diuretic 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 loss of potassium, magnesium and bicarbonate.

LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

PHARMACOKINETICS

Losartan

Absorption

Following oral administration, losartan 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 losartan was administered with a standardised meal.

Distribution

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

Metabolism

About 14 % of an intravenously- or orally-administered dose of losartan is converted to its active metabolite.

Elimination

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 potassium 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.

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 faeces.

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 metabolite can be removed by haemodialysis.

HYDROCHLOROTHIAZIDE

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. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

LOSARTAN POTASSIUM-HYDROCHLOROTHIAZIDE

In a pharmacokinetic interaction study, hydrochlorothiazide 12,5 mg did not alter the pharmacokinetics of losartan 50 mg and vice versa.

INDICATIONS

FORTZAAR is indicated for the treatment of hypertension in patients established on identical doses of the individual agents.

CONTRA-INDICATIONS

- Sensitivity to any of the components of FORTZAAR
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Severe renal function impairment (creatinine clearance less than 30ml/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride
- Porphyria
- Thiazide diuretics in (fixed dose) combination as with FORTZAAR, should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with FORTZAAR may lead to toxic blood concentrations of lithium
- Pregnancy and lactation (see **PREGNANCY AND LACTATION)**
- Hepatic impairment

Paediatric Use: Safety and efficacy in children has not been established.

WARNINGS

See **SPECIAL PRECAUTIONS**

Hypotension and electrolyte/fluid imbalance

In patients who are intravascularly volume-depleted (e.g.those treated with high-dose diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of FORTZAAR, or a lower starting dose should be used (see **DOSAGE AND DIRECTIONS FOR USE**). Periodic determination of serum electrolytes must be performed at appropriate intervals

Metabolic and endocrine effects

Hydrochlorothiazide, component of FORTZAAR, therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see **INTERACTIONS**).

Hydrochlorothiazide, component of FORTZAAR, may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. FORTZAAR should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide, a component of FORTZAAR, therapy. Hydrochlorothiazide, a component of FORTZAAR, therapy may precipitate hyperuricaemia and/or gout in certain patients.

Concomitant use with Lithium

Concomitant administration of lithium with FORTZAAR may lead to toxic blood concentrations of lithium (see **INTERACTIONS)**

INTERACTIONS

LOSARTAN POTASSIUM

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

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

Lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are co-administered with FORTZAAR.

Non-steroidal anti-inflammatory medicines (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of FORTZAAR

In patients with compromised renal function who are being treated with non-steroidal anti-inflammatory medicines (NSAIDs), the co-administration of FORTZAAR may result in a further deterioration of renal function.

HYDROCHLOROTHIAZIDE

When administered concurrently the following medication may interact with thiazide diuretics:
Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur.

Antidiabetic medication (oral agents and insulin): dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medication: additive effect or potentiation

Cholestyramine and colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastro-intestinal tract by up to 85 and 43 percent, respectively. FORTZAAR should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH: intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. norepinephrine): possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants: response to nondepolarising agents may be increased

Lithium: should not generally be given with FORTZAAR. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with FORTZAAR.

Non-steroidal anti-inflammatory medication 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 FORTZAAR.

PREGNANCY AND LACTATION

Pregnancy: When pregnancy is detected or suspected FORTZAAR should be discontinued as soon as possible. FORTZAAR should not be used in pregnancy as teratogenicity has been shown in experimental animals.

Thiazides such as in FORTZAAR cross the placental barrier and appear in cord blood. The use of FORTZAAR in otherwise healthy pregnant women is contra-indicated.

Women of childbearing age should ensure adequate barrier contraception.

Lactation

Safety in breastfeeding has not been established. Thiazides appear in human milk.

DOSAGE AND DIRECTIONS FOR USE

The maximum dose is one tablet of FORTZAAR (100 mg losartan potassium and 25 mg hydrochlorothiazide) once daily. The maximum 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).

FORTZAAR is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see **SPECIAL PRECAUTIONS).**

FORTZAAR should not be used as initial therapy in elderly patients.

FORTZAAR may be administered with other antihypertensive agents, such as calcium channel blockers and beta-blockers.

FORTZAAR may be administered with or without food.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with FORTZAAR and are shown in decreasing order of frequency within body system:

Very common (≥1/10), Common (≥ 1/100, <1/10), Uncommon (≥1/1,000, <1/100) and Rare (≥1/10,000, <1/1,000)

Nervous system disorders:

Common: dizziness

General disorders and administration site conditions:

Common: asthenia/fatigue

Losartan:

In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with losartan potassium and are shown in decreasing order of frequency within body system:

Very common (≥1/10), Common (≥ 1/100, <1/10), Uncommon (≥1/1,000, <1/100) and Rare (≥1/10,000, <1/1,000)

Infections and infestations:

Common: upper respiratory infection

Psychiatric disorders:

Common: insomnia

Nervous system disorders:

Very common: headache

Common: dizziness

Cardiac disorders:

Common: palpitation, tachycardia

Vascular disorders:

Uncommon: orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:

Common: cough, pharyngitis, nasal congestion, sinus disorder

Gastro-intestinal disorder:

Common: diarrhoea, nausea, abdominal pain, dyspepsia

Skin and subcutaneous tissue disorders:

Uncommon: rash

Musculoskeletal, connective tissue and bone disorders:

Common: back pain, muscle cramps

General disorders and administration site conditions:

Common: asthenia/fatigue, oedema/swelling, chest pain

Investigations:

Common: hyperkalaemia, elevations of ALT

Hydrochlorothiazide:

In controlled clinical trials for essential hypertension, the following adverse experiences were reported in patients treated with hydrochlorothiazide and are shown in decreasing order of frequency within body system:

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: Common: (≥1/100, <1/10), Uncommon; (≥1/1,000, <1/100), Rare: (≥1/10,000, <1/1,000), Very Rare: (>1/10,000, including isolated reports).

Blood and the lymphatic system disorders:

Rare: thrombocytopenia

Very rare: leukopenia; agranulocytosis; haemolytic anaemia

Metabolic and nutrition disorders:

Uncommon: anorexia; hyperuricaemia

Rare: hyperglycaemia

Nervous System Disorders:

Rare: paraesthesia; headache

Vascular Disorders:

Uncommon: hypotension, (including orthostatic hypotension)

Respiratory, thoracic and mediastinal disorders:

Very rare: respiratory distress including pneumonitis and pulmonary oedema

Gastro-intestinal Disorders:

Uncommon: nausea; vomiting

Rare: diarrhoea; constipation

Very rare: pancreatitis

Hepato-Biliary disorders:

Rare: jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders:

Uncommon: rash; urticaria

Rare: photosensitivity

Very rare: necrotising angiitis (vasculitis and cutaneous vasculitis)

Renal and urinary disorders:

Rare: glycosuria

The following clinical trials side effects have been reported with the use of either losartan or hydrochlorothiazide but the frequencies are unknown:

Infections and infestations:

Sialadenitis

Blood and the lymphatic system disorders:

Aplastic anaemia

Metabolic and nutrition disorders:

Electrolyte imbalance including hyponatraemia and hypokalaemia

Psychiatric disorders:

Restlessness

Eye disorders:

Xanthopsia, transient blurred vision

Ear and labyrinth disorders:

Vertigo

Vascular disorders:

Hypotension and/or postural hypotension

Gastro-intestinal disorders:

Gastric irritation

Skin and subcutaneous tissue disorders:

Purpura

Musculoskeletal, connective tissue and bone disorders:

Cramping, muscle spasm

Renal and urinary disorders:

Renal dysfunction, interstitial nephritis, renal failure

General disorders and administration site conditions:

Fever, weakness

Post-marketing experience:

The following adverse reactions have been reported in post-marketing experience; they are derived from spontaneous reports for which precise incidences cannot be determined therefore, the frequency is unknown:

Blood and the lymphatic system disorders:

Thrombocytopenia

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 in patients treated with FORTZAAR; some of these patients previously experienced angioedema with other medicines including ACE inhibitors.

Musculoskeletal, connective tissue, and bone disorders:

Arthralgia (reported with losartan)

Nervous system disorders:

Dysgeusia (reported with losartan)

Vascular disorders:

Vasculitis, including Henoch-Schoenlein purpura

Respiratory, thoracic and mediastinal disorders:

Cough

Gastro-intestinal disorders:

Diarrhoea, vomiting

Hepato-biliary disorders:

Hepatitis

Skin and subcutaneous tissue disorders:

Urticaria, erythroderma has been reported with losartan.

Photosensitivity has been reported with FORTZAAR

SPECIAL PRECAUTIONS

Hepatic and renal impairment

FORTZAAR is not recommended for patients with hepatic impairment or severe renal impairment (see **DOSAGE AND DIRECTIONS FOR USE and CONTRA-INDICATIONS)**.

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported. These changes in renal function may be reversible upon discontinuation of therapy. FORTZAAR 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 (see **CONTRA-INDICATIONS**).

Other

In patients receiving hydrochlorothiazide, a component of FORTZAAR, 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 hydrochorothiazide, as contained in FORTZAAR.

Excipient

FORTZAAR contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take FORTZAAR**.**

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data to suggest that FORTZAAR affects the ability to drive and use machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

LOSARTAN POTASSIUM

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m^2) and 2000 mg/kg (11800 mg/m^2) (500 and 1000 times ** the maximum recommended daily human dose), respectively.

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 haemodialysis.

HYDROCHLOROTHIAZIDE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalaemia may accentuate cardiac dysrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

IDENTIFICATION

FORTZAAR tablets are light yellow, oval shaped, film-coated tablets, with "747" on one side and plain on the other side.

PRESENTATION

FORTZAAR tablets are supplied in blister packs of 30.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Keep well closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

34/7.1.3/0281

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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*[*] Based on a patient weight of 50 kg