SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

COZAAR® COMP 50/12,5 Tablet

COZAAR® COMP 100/12,5 Tablet

COMPOSITION

Each COZAAR COMP 50/12,5 Tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.

COZAAR COMP 50/12,5 contains 4,24 mg (0,108 mEq) of potassium.

Inactive Ingredients: microcrystalline cellulose (E460), pregelatinised maize starch, magnesium stearate (E572), hydroxypropyl cellulose, hypromellose (E464), titanium dioxide, carnauba wax, quinolone yellow aluminium lake, lactose monohydrate.

Each COZAAR COMP 100/12,5 Tablet contains 100 mg losartan potassium and 12,5 mg hydrochlorothiazide.

COZAAR COMP 100/12,5 contains 8,48 mg (0,216 mEq) of potassium.

Inactive Ingredients: microcrystalline cellulose (E460), pregelatinised maize starch, magnesium stearate (E572), hydroxypropyl cellulose, hypromellose (E464), titanium dioxide, carnauba wax, lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION

A.7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

COZAAR COMP (losartan potassium-hydrochlorothiazide) combines an angiotensin II receptor (type AT_1) antagonist and a diuretic, hydrochlorothiazide.

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.

Losartan binds selectively to the AT_1 receptor and does not bind to or block other hormone receptors or ion channels important in cardiovascular regulation. Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin.

Hydrochlorothiazide

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Hydrochlorothiazide is a diuretic and antihypertensive agent. It 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, magnesium and bicarbonate.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Losartan potassium - Hydrochlorothiazide

Losartan and hydrochlorothiazide are additive in their antihypertensive efficacy.

Pharmacokinetic properties

Absorption

Losartan

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 to 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 to 9 hours, respectively.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled 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

The plasma half-life ranges between 5,6 and 14,8 hours. Hydrochlorothiazide is eliminated unchanged 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

COZAAR COMP is indicated for the treatment of hypertension in patients established on identical doses of the individual medicines.

CONTRAINDICATIONS

- Hypersensitivity to losartan or hydrochlorothiazide or any of the components of COZAAR COMP.
- 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 < 30 ml/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 (see **INTERACTIONS**).
- Porphyria.
- Hydrochlorothiazide in combination with COZAAR COMP should not be given to patients with Addison's disease.
- COZAAR COMP is also contraindicated in patients with anuria, and hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with COZAAR COMP may lead to toxic blood concentrations of lithium.

- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Use of medicines that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces foetal renal function and increases foetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with foetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure and death. When pregnancy is detected, discontinue COZAAR COMP as soon as possible (see **PREGNANCY AND LACTATION**).
- Hepatic impairment.
- The concomitant use of COZAAR COMP with aliskiren-containing products is contraindicated (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**)

WARNINGS AND SPECIAL PRECAUTIONS

Should a woman become pregnant while receiving COZAAR COMP, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see **CONTRAINDICATIONS** and **PREGNANCY AND LACTATION**).

Hypersensitivity: Angioedema (see **SIDE EFFECTS**).

Hepatic and renal impairment

COZAAR COMP is not recommended for patients with hepatic impairment or severe renal impairment (see **DOSAGE AND DIRECTIONS FOR USE** and **CONTRAINDICATIONS**).

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 not be reversible upon discontinuation of therapy.

COZAAR COMP may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see **CONTRAINDICATIONS**).

Increases in serum potassium

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

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 COZAAR COMP or a lower starting dose should be used (see **DOSAGE AND DIRECTIONS FOR USE**). Periodic determination of serum electrolytes should be performed at appropriate intervals.

Metabolic and endocrine effects

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

Hydrochlorothiazide as in COZAAR COMP may decrease urinary calcium excretion and may cause an elevation of serum calcium. Marked hypercalcaemia may be evidence of occult hyperparathyroidism. COZAAR COMP should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide therapy. COZAAR COMP may precipitate hyperuricaemia and/or gout in certain patients.

Concomitant use with Lithium

Concomitant administration of lithium with COZAAR COMP may lead to toxic blood concentrations of lithium (see **CONTRAINDICATIONS**).

Other

In patients receiving hydrochlorothiazide as in COZAAR COMP, 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.

Paediatric Use

Safety and efficacy in children has not been established.

Dual blockade of renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren may increase the risk of hypotension, hyperkalaemia and decrease renal function (including acute renal failure). Dual blockade of RAAS through the combined use of COZAAR COMP and aliskiren is therefore not recommended. COZAAR COMP should not be used concomitantly with aliskiren (see **CONTRAINDICATIONS**).

Effects on ability to drive and use machines

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

Excipient

COZAAR COMP contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take COZAAR COMP.

INTERACTIONS

Losartan potassium

In clinical pharmacokinetic trials no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbitone (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.

Concomitant use of medicines that block angiotensin II or its effects and 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.

Lithium excretion may be reduced (see **CONTRAINDICATIONS**).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive medicines. Therefore, the antihypertensive effect of COZAAR COMP 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 COZAAR COMP may result in a further deterioration of renal function, including possible acute renal failure. 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 such as COZAAR COMP, ACE inhibitors and/or aliskiren is associated with increased risks of

hypotension, syncope, hyperkalaemia and changes in renal function (including acute renal failure) compared to monotherapy. Do not co-administer aliskiren with COZAAR COMP in patients with diabetes. Avoid use of aliskiren with COZAAR COMP in patients with renal impairment (GFR < 60 ml/min) (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Hydrochlorothiazide

When administered concurrently the following medication may interact with thiazide diuretics:

Alcohol, barbiturates or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic medicines (oral medicines and insulin): Dosage adjustment of the antidiabetic medicine may be required.

Other antihypertensive medicines: 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 gastrointestinal tract by up to 85 and 43 %, respectively. COZAAR COMP should therefore be administered one hour before the intake of the resin.

Corticosteroids, ACTH or glycyrrhizin (found in liquorice): 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, nondepolarising (e.g. pancuronium): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not be given with COZAAR COMP (see **CONTRAINDICATIONS**).

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 loop, potassium-sparing and thiazide diuretics.

The use of COZAAR COMP is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take COZAAR COMP during pregnancy (see **CONTRAINDICATIONS**). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with COZAAR COMP should be stopped immediately and if appropriate, alternative therapy should be started. Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations. COZAAR COMP passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of COZAAR COMP during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see **CONTRAINDICATIONS**).

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established (see **CONTRAINDICATIONS**). When pregnancy is planned or confirmed COZAAR COMP should be discontinued.

Medicines affecting the renin-angiotensin system, such as COZAAR COMP, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Women of childbearing age should ensure effective contraception.

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 foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxaemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxaemia.

Women of childbearing age should ensure adequate contraception.

Lactation

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

DOSAGE AND DIRECTIONS FOR USE

The usual starting and maintenance dose of COZAAR COMP is one tablet of COZAAR COMP 50/12,5 (losartan 50 mg/hydrochlorothiazide 12,5 mg) once daily. For patients who do not respond adequately to COZAAR COMP 50/12,5 the dosage may be increased to two tablets of COZAAR COMP 50/12,5 once daily. The maximum dose is two tablets of COZAAR COMP 50/12,5 once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy. COZAAR COMP 100/12,5 is available for those patients titrated to 100 mg of COZAAR who require additional blood pressure control.

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

COZAAR COMP is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see **WARNINGS AND SPECIAL PRECAUTIONS** and **CONTRAINDICATIONS**).

No initial dosage adjustment of COZAAR COMP is necessary for elderly patients. A higher dose (100 mg losartan potassium and 25 mg hydrochlorothiazide) should not be used as initial therapy in elderly patients.

COZAAR COMP may be administered with other antihypertensive agents, particularly calcium channel blockers and beta-blockers.

COZAAR COMP may be administered with or without food.

SIDE EFFECTS

Clinical trials

COZAAR COMP

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

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000), including isolated reports.

Nervous system disorders

Common: dizziness

General disorders and administration site conditions

Common: asthenia/fatigue.

Losartan Potassium

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 (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000), including isolated reports.

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, upper respiratory infection

Gastrointestinal 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

Reproductive system and breast disorders

Erectile dysfunction/impotence

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: Very common (≥ 1/10), 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

Gastrointestinal disorders

Uncommon: nausea, vomiting

Rare: diarrhoea, constipation

Very rare: pancreatitis

Hepatobiliary 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.

Post-marketing data

Blood and the lymphatic system disorders

Aplastic anaemia, 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 have been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other medicines including ACE inhibitors.

Metabolic and nutrition disorders

Electrolyte imbalance including hyponatraemia and hypokalaemia

Psychiatric disorders

Restlessness

Nervous system disorders

Dysgeusia (reported with losartan)

Eye disorders

Xanthopsia, transient blurred vision

Ear and labyrinth disorders

Vertigo

Vascular disorders

Hypotension, vasculitis, including Henoch-Schoenlein purpura

Respiratory, thoracic and mediastinal disorders

Cough

Gastrointestinal disorders

Gastric irritation, sialoadenitis, diarrhoea, vomiting

Hepatobiliary disorders

Hepatitis

Skin and subcutaneous tissue disorders

Purpura (including Henoch-Schoenlein purpura), pruritus, toxic epidermal necrolysis, cutaneous lupus erythematosus, urticaria, erythroderma have been reported with losartan, photosensitivity

Musculoskeletal, connective tissue and bone disorders

Cramping, muscle spasm, myalgia, arthralgia (reported with losartan)

Renal and urinary disorders

Renal dysfunction, interstitial nephritis, renal failure

General disorders and administration site conditions

Fever, weakness, malaise

Investigations

Liver function abnormalities.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Losartan potassium

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

COZAAR COMP 50/12,5 Tablets are yellow, oval shaped, film-coated tablets, with 717 on one side and scored on the other side.

COZAAR COMP 100/12,5 Tablets are white, oval-shaped, film-coated tablets with 745 on one side and plain on the other.

PRESENTATION

COZAAR COMP 50/12,5 Tablets are supplied in white, opaque PVC/PE/PVDC blisters with aluminium foil lidding in cartons containing 30 tablets.

COZAAR COMP 100/12,5 Tablets are supplied in white, opaque PVC/PE/PVDC blisters with aluminium foil lidding in cartons containing 30 tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Keep blister in carton until required for use. Protect from moisture. Keep out of reach of children.

REGISTRATION NUMBERS

COZAAR COMP 50/12,5: 30/7.1.3/0284

COZAAR COMP 100/12,5: 46/7.1.3/0865

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

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