Revision Date: 30-11-2025

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

COZAAR® 50 Tablet

COZAAR® 100 Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of COZAAR 50 contains 50 mg losartan potassium.

Each tablet of COZAAR 100 contains 100 mg losartan potassium.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

COZAAR 50 is a white oval shaped film-coated tablet, scored one side, engraved ‘952’ on the other side.

COZAAR 100 is a white, teardrop-shaped, film-coated tablet with ‘960’ debossed on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

COZAAR is indicated for:

- the treatment of hypertension
- renal protection in Type 2 diabetic patients with hypertension and proteinuria

4.2 Posology and method of administration

Hypertension

The usual starting and maintenance dose is 50 mg once daily. It should be noted that the maximal antihypertensive effect is attained 3 to 6 weeks after initiation of therapy. The dose may be increased to 100 mg once daily thereafter.

Renal protection in type 2 diabetic patients with hypertension and proteinuria

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. COZAAR may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycaemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

Special populations

Use in patients with intravascular volume-depletion

For patients with intravascular volume-depletion (e.g., those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see Section 4.4).

Use in elderly patients and in patients with renal or hepatic impairment

No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis. A lower dose should be considered for patients

with a history of hepatic impairment (see Section 4.4).

Paediatric population

The safety and efficacy of children aged 6 months to less than 6 years has not been established.

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients 6 to 16 years of age weighing more than or equal to 20 to less than 50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients 6 to 16 years of age weighing more than or equal to 50 kg, the recommended dose is 50 mg once daily. The dose can be increased to a maximum of 100 mg once daily.

If paediatric patients are intravascularly volume depleted, these conditions should be corrected prior to administration of COZAAR.

COZAAR is contraindicated in paediatric patients with glomerular filtration rate less than 30 mL/min/1,73 m^2 and in paediatric patients with hepatic impairment.

Method of administration

COZAAR may be administered with or without food.

COZAAR may be administered with other antihypertensive agents.

4.3 Contraindications

- Hypersensitivity to any of the components of COZAAR
- 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)
- Hepatic impairment
- Severe renal function impairment (creatinine clearance less than 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
- Porphyria
- Lithium therapy: concomitant administration with COZAAR may lead to toxic blood concentrations of lithium
- Pregnancy and lactation (see Section 4.6)
- COZAAR should not be administered with aliskiren in patients with diabetes (see Section 4.5).
- Concomitant use of fluoroquinolones with ACE inhibitors/Renin-Angiotensin Receptor blockers is contraindicated in patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving COZAAR, the treatment must be stopped promptly and changed to a different medicine (see Section 4.6). If a woman is contemplating pregnancy, a different class of medicine should be used (see Section 4.6).

Foetal toxicity

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 as soon as possible (See Section 4.6).

Hypersensitivity

Angioedema (see Section 4.8).

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan, a component of COZAAR (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, COZAAR should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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, or a lower starting dose should be used (see Section 4.2).

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalaemia was higher in the group treated with

COZAAR as compared to the placebo group; however, few patients discontinued therapy due to hyperkalaemia (see Section 4.8).

Concomitant use of other medicines that may increase serum potassium may lead to hyperkalaemia (see section 4.5).

Serum potassium levels should be monitored regularly.

Liver function impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a dose of 25 mg should be considered for patients with a history of hepatic impairment (see Section 4.2).

Renal function impairment

When impaired renal function is present, changes in renal function as a consequence of inhibiting the renin-angiotensin system including renal failure, have been reported in susceptible individuals; in some patients these changes in renal function may be reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive uremia and (less frequently) with acute renal failure and/or death. Similar outcomes have been reported with COZAAR.

Agents that affect the renin-angiotensin system such as COZAAR may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery

to a solitary kidney. These changes in renal function may be reversible upon discontinuation of therapy.

Porphyria

Limited information is available regarding the effect of antihypertensive medication in patients with porphyria. Safety of losartan in patients with porphyria has not been fully established.

Use in the elderly

In clinical studies there was no age-related difference in efficacy or safety profile of losartan.

Paediatric population

Neonates with a history of *in utero* exposure to COZAAR:

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.

Concomitant use of fluoroquinolones and ACE inhibitors/Renin-Angiotensin Receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see Section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/Renin-Angiotensin Receptor blockers.

Excipient

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

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Interactions

In clinical pharmacokinetic trials, no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole and erythromycin. Rifampicin and fluconazole reduce the levels of the active metabolite of COZAAR. The clinical consequences of these interactions have not been evaluated.

As with other medicines that block angiotensin II or its effects such as COZAAR, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium, or other medicines that may increase serum potassium (e.g., trimethoprim-containing products), may lead to increases in serum potassium.

Lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with COZAAR (see Section 4.3).

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclo-oxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive medicines. Therefore, the antihypertensive effect of angiotensin II receptor antagonists such as COZAAR or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

Co-administration of angiotensin II receptor antagonists such as COZAAR with NSAIDS or ACE inhibitors may result in a 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, hyperkalaemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on COZAAR and other agents that affect the RAAS. Do not co-administer aliskiren with COZAAR in patients with diabetes. Avoid use of aliskiren with COZAAR in patients with renal impairment (GFR < 60 mL/min).

Concomitant use of fluoroquinolones and ACE inhibitors/Renin-Angiotensin Receptor blockers may precipitate acute kidney injury (see Section 4.3).

Grapefruit juice contains components that inhibit CYP 450 enzymes and may lower the concentration of the active metabolite of COZAAR which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking COZAAR.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing age should ensure adequate contraception.

Female patients of childbearing age should be told about the consequences of exposure to COZAAR during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their medical practitioners as soon as possible.

Pregnancy

COZAAR is contraindicated in pregnancy.

Medicines that act directly on the renin-angiotensin system can cause injury and death to the developing foetus. When pregnancy is detected, discontinue COZAAR as soon as possible.

Although there is no experience with the use of COZAAR in pregnant women, animal studies with losartan potassium have demonstrated foetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, foetal renal perfusion which is dependent upon the development of the renin-angiotensin system, begins in the second trimester; thus risk to the foetus increases if COZAAR is administered during the second or third trimesters of pregnancy.

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 as soon as possible.

These adverse outcomes are usually associated with the use of these medicines in the second and third trimesters of pregnancy. Most epidemiologic studies examining foetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished medicines affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimise outcomes for both mother and foetus.

Breastfeeding

It is not known whether losartan is excreted in breastmilk. Safety of breastfeeding in mothers taking COZAAR has not been established. However, significant levels of losartan and the active metabolite were shown to be present in rat milk (see Section 4.3).

Fertility

No human data is available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions from clinical trials

In controlled clinical trials for essential hypertension, the following adverse experiences were reported:

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, vertigo

Cardiac disorders:

Common: palpitation, tachycardia

Vascular disorders:

Uncommon: orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:

Common: cough, pharyngitis, nasal congestion, sinus disorder

Gastrointestinal disorders:

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

Adverse reactions from spontaneous reporting

Post-marketing

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 lymphatic system disorders:

Anaemia

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 ACE inhibitors and angiotensin receptor blockers.

Nervous system disorders:

Migraine, dysgeusia

Reproductive system and breast disorders:

Erectile dysfunction/impotence

Vascular disorders:

Vasculitis, including Henoch-Schönlein purpura

Respiratory, thoracic and mediastinal disorders:

Cough

Hepatobiliary disorders:

Hepatitis

Skin and subcutaneous tissue disorders:

Urticaria, pruritus, erythroderma, photosensitivity

Musculoskeletal, connective tissue and bone disorders:

Myalgia, arthralgia

Investigations:

Liver function abnormalities

Haematological disorders:

Thrombocytopenia (reported rarely)

Gastrointestinal disorders:

Vomiting, intestinal angioedema (reported rarely)

General disorders and administration site conditions:

Malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 7.1.3 Other hypotensives

5.1 Pharmacodynamic properties

Mechanism of action

Losartan, an angiotensin receptor blocker (ARB), 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 which is a vasoconstrictor, regardless of the source or route of synthesis.

Losartan is a specific antagonist of the angiotensin II receptor type AT_1. Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin.

During losartan administration the removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to a 2 to 3-fold increase in angiotensin II in plasma. However, antihypertensive activity and suppression of plasma aldosterone concentration were apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and

angiotensin II levels declined to untreated levels within 3 days.

In non-diabetic hypertensive patients with proteinuria (2 g or more/24 hours) treated for 8 weeks, the administration of losartan 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.

5.2 Pharmacokinetic properties

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 after 1 hour and after 3 to 4 hours, respectively.

Distribution

Both losartan and its active metabolite are 99 % or more bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Metabolism

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

Elimination

Plasma clearance of losartan and the 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 doses up to 200 mg.

Following oral administration in normal volunteers, plasma concentrations of losartan and its active metabolite decline poly-exponentially 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.

Characteristics in patients with hepatic and renal impairment

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 healthy 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 haemodialysis patients. Plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients. Neither losartan nor the active metabolite can be removed by haemodialysis.

Paediatric population

Short-term antihypertensive effects of COZAAR have been demonstrated in limited numbers of hypertensive paediatric patients aged 6 years to 16 years.

In a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age,

patients who weighed more than or equal to 20 kg to less than 50 kg, received either 2,5; 25 or 50 mg of losartan daily, and patients who weighed more than or equal to 50 kg received either 5, 50 or 100 mg of losartan daily. Losartan administration once daily lowered trough blood pressure in a dose-dependent manner. The dose response to losartan was observed across all subgroups (e.g., age, Tanner stage, gender, race). However, the lowest doses studied, 2,5 mg and 5 mg, corresponding to an average daily dose of 0,07 mg/kg, did not appear to offer consistent antihypertensive efficacy. In this study, COZAAR was generally well tolerated.

The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

COZAAR contains the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinised starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, titanium dioxide and carnauba wax.

COZAAR contains lactose hydrous.

6.2 Shelf life

36 months.

6.3 Special precautions for storage

Store in a dry place at or below 30 °C. Keep container tightly closed.

6.4 Nature and contents of container

COZAAR 50 tablets are available in blister packs of 30.

COZAAR 100 tablets are available in opaque white blister packs of 30.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Organon South Africa (Pty) Ltd

Spaces, 1st Floor

22 Magwa Crescent, Gateway West

Waterfall City, Midrand, 2090

South Africa

8 REGISTRATION NUMBER(S)

COZAAR 50: 29/7.1.3/0268

COZAAR 100: 36/7.1.3/0490

~~9~~ DATE OF FIRST AUTHORISATION

COZAAR 50: 31 October 1995

COZAAR 100: 30 November 2007

10 DATE OF REVISION OF THE TEXT

30 November 2025

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