SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

COZAAR® Tablet

COZAAR® 100 Tablet

COMPOSITION

Each tablet of COZAAR contains 50 mg losartan potassium

Each tablet of COZAAR 100 contains 100 mg losartan potassium

Contains lactose

PHARMACOLOGICAL CLASSIFICATION

A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION

MECHANISM OF ACTION

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 or route 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. Furthermore, losartan does not inhibit ACE

(kininase II), the enzyme that degrades bradykinin. Consequently, effects not directly related to blocking the AT_1 receptor, such as the potentiation of bradykinin-mediated effects or the generation of oedema are not associated with losartan.

RENAAL STUDY

The Reduction of Endpoints in NIDDM with the Losartan (RENAAL) study was a placebo-controlled, double-blind study conducted worldwide in 1513 type 2 diabetic patients (751 treated with COZAAR) with proteinuria and mostly (97 %) with hypertension. The goal of the study was to demonstrate the renal protective effects of COZAAR over and above the benefits of blood pressure control alone. Patients with proteinuria and serum creatinine of 1,3 to 3,0 mg/dl were randomized to receive COZAAR 50 mg once daily titrated according to blood pressure response, or placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg once daily as appropriate; 72 % of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Patients were followed for up to 4,6 years (mean of 3,4 years).

The primary endpoint of the study was the composite endpoint of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation) or death. The endpoint was reached in 327 patients (43,5 % of total 751 patients) given losartan versus 359 (47,1 % of the total 762 patients) given placebo. For unadjusted event rates, the absolute risk reduction was 3,6 % (47,1 vs. 43,5 %), losartan treatment resulted in an estimated reduction in the primary composite endpoint by 16,1% (p=0,022). The 95,2 % confidence interval for the risk reduction was (2,3 %, 27,9 %). The following results were found in the group treated with COZAAR: 25,3 % risk reduction in doubling of serum creatinine (p=0,006); 28,6 % risk reduction in end-stage renal disease (p=0,002); 19 % risk reduction in end-stage renal disease or death (p=0,009); 21,0 % risk reduction in doubling of serum creatinine or end-stage renal disease (p=0,010). The rate of the all-cause deaths component was not significantly different between the two treatment groups.

The secondary endpoints of the study were: change in proteinuria; the rate of progression of renal disease and the composite of morbidity and mortality from cardiovascular causes (hospitalization for heart failure, myocardial infarction, revascularization, stroke, hospitalization for unstable angina or cardiovascular death). The results showed an average reduction of 34,3 % in the level of proteinuria in the group treated with COZAAR (p less than 0,001). Treatment with COZAAR reduced the rate of

decline in renal function during the chronic phase of the study by 13,9 %, p=0,003 (median rate of decline of 18,5 %, p=0,01) as measured by the reciprocal of the serum creatinine concentration. There was no significant difference between the group treated with COZAAR (247 events) and the placebo group (268 events) in the composite endpoint of cardiovascular morbidity and mortality.

PHARMACOKINETICS

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 to 4 hours, respectively.

Distribution

Both losartan and its active metabolite are bound to plasma proteins by 99 % or more, 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 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 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-labeled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces. Following an intravenous dose of ^{14}C-labeled losartan in man, about 43 % of radioactivity is recovered in the urine and 50 % in the faeces.

Characteristics in Patients

Following oral administration in patients with mild to moderate alcoholic cirrhosis of the liver, plasma concentrations of losartan and its active metabolite were, respectively, 5-fold and 1,7-fold greater than those seen in young male volunteers.

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC for losartan is approximately 2-fold greater in 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.

PHARMACODYNAMICS

During losartan administration, removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to 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.

Losartan is a specific antagonist of the angiotensin II receptor type AT_1, it does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. This provides a pharmacodynamic distinction between losartan and ACE inhibitors.

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

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.

INDICATIONS

HYPERTENSION

COZAAR is indicated for the treatment of hypertension.

RENAL PROTECTION IN TYPE 2 DIABETIC PATIENTS WITH HYPERTENSION AND PROTEINURIA

CONTRA-INDICATIONS

COZAAR is contra-indicated in patients

- Who are hypersensitive to any component of this product
- With a history of angio-oedema related to ACE-inhibitors or angiotensin receptor antagonists such as COZAAR
- Hypertrophic obstructive cardiomyopathy
- COZAAR is not recommended for patients with severe renal impairment or for patients with hepatic impairment
- Aortic stenosis, left ventricular outflow track obstruction
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene and amiloride
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**)

Paediatric Use:

Safety and effectiveness in children have not been established.

WARNINGS

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

Serum potassium levels should be monitored regularly.

INTERACTIONS

In clinical pharmacokinetic trials, no interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, 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 or salt substitutes containing potassium, may lead to increases in serum potassium.

As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.
Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclo-oxygenase-2 inhibitors (COX-2 inhibitors) may reduce the effect of diuretics and other antihypertensive drugs. Therefore, the antihypertensive effect of angiotensin II receptor antagonists or ACE inhibitors may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g. elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclo-oxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in a further deterioration of renal

function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

PREGNANCY AND LACTATION

Pregnancy

When pregnancy is detected, COZAAR should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals.

Women of childbearing age should ensure adequate contraception.

Breast feeding mothers

It is not known whether losartan is excreted in human milk. Safety of breast feeding 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 **CONTRA-INDICATIONS)**.

DOSAGE AND DIRECTIONS FOR USE

COZAAR may be administered with or without food.

COZAAR may be administered with other antihypertensive agents.

HYPERTENSION

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3 to 6 weeks after initiation of therapy. The dose may be increased to 100 mg once daily.

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 **SPECIAL PRECAUTIONS**).

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 **SPECIAL PRECAUTIONS**).

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).

SIDE EFFECTS AND SPECIAL PRECAUTIONS

SIDE EFFECTS

In controlled clinical trials for essential hypertension, the following adverse experiences were reported, regardless of drug relationship, and are shown in decreasing order of frequency within body system:

[Very common (more than or equal to 1/10), Common (more than or equal to 1/100, less than 1/10), Uncommon (more than or equal to 1/1 000, less than 1/100) and Rare (more than or equal to 1/10 000, less than 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

Gastro-intestinal 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

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, angio-oedema 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 angio-oedema 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)

Gastro-intestinal:

Vomiting

General disorders and administration site conditions:

Malaise

SPECIAL PRECAUTIONS

Hypersensitivity: Angio-oedema (see **SIDE EFFECTS**)

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 **DOSAGE AND DIRECTIONS FOR USE**).

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 **SIDE EFFECTS**).

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 **DOSAGE AND DIRECTIONS FOR USE**).

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 azotemia and (less frequently) with acute renal failure and/or death. Similar outcomes have been reported with COZAAR.

Agents 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 COZAAR; 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.

Effects on Ability to Drive and Use Machines

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

COZAAR 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.

PRESENTATION

COZAAR tablets are available in blister packs of 30.

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

STORAGE INSTRUCTIONS

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

COZAAR: 29/7.1.3/0268

COZAAR 100: 36/7.1.3/0490

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

MSD (Pty) Ltd

16th Road

Halfway House

1685

DATE OF PUBLICATION OF THIS PACKAGE INSERT

30 November 2008 (Revised: 15 January 2010)

WPC-CZR-T-082009

ATTACHMENT 3
TRACKING OF SOURCE DOCUMENTS

Product name: Cozaar and Cozaar 100 Tablets (Combined)				
Component description: Package Insert				
Reference number: YM20091215				
Date of Publication/Implementation: 15 January 2010				
	Version number	**Date**		**Comments**
		To AC	**From AC**	
		1 July 2009	25 August 2009	USRN project source docs proofreading and translation by the third party (Prof) (ACR not filled in)
	0	8 September 2009	9 September 2009	Had to send back to Merck for review after translation before preparing source docs because of an additional WPC update (WPC-082009)
	1	11 September 2009	17 September 2009	Editorial changes
	2	28 September 2009	2 December 2009	No change/corrections. Only changed the revision number so that have the same version on all components as there are editorial changes in the PIL.
	3	8 December 2009		Editorial. Changed the date of submission to 15 December 2009