AUSTRALIAN PRODUCT INFORMATION

COZAVAN®

(losartan potassium)

1 NAME OF THE MEDICINE

Losartan potassium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COZAVAN film-coated tablet contains 25 mg or 50 mg of losartan potassium as the active ingredient.

Excipients with known effect: lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

COZAVAN 25 mg film-coated tablet – white to off white, oval shaped biconvex film-coated tablet with "A" engraved on one side and "25" on the other side

COZAVAN 50 mg film-coated tablet – white to off white, oval shaped biconvex film-coated tablet with "A50" engraved on one side and a central break line on the other side

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension

COZAVAN is indicated for the treatment of hypertension.

It may be used alone or in combination with other antihypertensive agents (e.g. thiazide diuretics).

Renal Protection in Type 2 Diabetic Patients with Proteinuria

COZAVAN is indicated to delay the progression of renal disease in hypertensive type 2 diabetics with proteinuria, defined as urinary albumin to creatinine ratio ≥ 300 mg/g.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

If the antihypertensive effect using 50 mg once daily is inadequate, 25 mg twice daily is recommended prior to increasing the dose.

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

COZAVAN can be administered once or twice daily. The total daily dose ranges from 25 mg to 100 mg.

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

COZAVAN may be administered with other antihypertensive agents.

COZAVAN may be administered with or without food.

4.3 CONTRAINDICATIONS

COZAVAN is contraindicated in pregnant women and in patients who are hypersensitive to any component of this product.

COZAVAN should not be administered with aliskiren in patients with diabetes (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fetal Toxicity

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue COZAVAN as soon as possible. See Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy.

Hypersensitivity

Angioedema (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE 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 COZAVAN, or a lower starting dose should be used (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 hyperkalemia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Effects on Laboratory Tests).

Concomitant use of other drugs that may increase serum potassium may lead to hyperkalaemia (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in Hepatic Impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in susceptible individuals. In patients whose renal function may depend on the activity of the renin-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 (rarely) with acute renal failure and/or death. Angiotensin II receptor antagonists would be expected to behave similarly.

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 potassium.

Use in the Elderly

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

Paediatric Use

Safety and effectiveness in children have not been established.

Effects on Laboratory Tests

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Effects on Laboratory Tests

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interactions of clinical significance have been identified. Compounds which have been studied in clinical pharmacokinetic trials include digoxin, warfarin, cimetidine and phenobarbital (phenobarbitone) and ketoconazole. Rifampicin and fluconazole have been reported to reduce levels of active metabolite. Clinical studies have shown that concomitant use of losartan and hydrochlorothiazide may lead to potentiation of the antihypertensive effects.

As with other drugs that block angiotensin II or its effect, concomitant use of 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.

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.

The antihypertensive effect of losartan may be attenuated by the non-steroidal anti-inflammatory drug indometacin.

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-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 cyclooxygenase-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 failure which is usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

These interactions should be considered in patients taking NSAIDs including selective COX-2 inhibitors concomitantly with diuretics and angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

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, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on losartan potassium and other agents that affect the RAAS. Do not co-administer aliskiren with losartan potassium in patients with diabetes. Avoid use of aliskiren with losartan potassium in patients with renal impairment (GFR < 60 mL/min).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Repeat-dose studies in animals did not show any evidence of toxic effect on the reproductive system, and no adverse effects on fertility were observed in male or female rats at oral doses of losartan potassium up to 150-200 mg/kg/day.

Use in Pregnancy

Pregnancy Category: D

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, COZAVAN should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Potential neonatal adverse effects include hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with skeletal deformations, fetal limb contractures, craniofacial deformation, fetal lung hypoplasia and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. When pregnancy is detected, discontinue COZAVAN as soon as possible.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of COZAVAN as soon as possible.

These adverse outcomes are usually associated with the use of these drugs in the second and third trimesters of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus. Although there is no experience with the use of COZAVAN in pregnant women, animal studies with losartan potassium have demonstrated fetal and neonatal injury and death, the mechanism of which is believed to be pharmacologically mediated through effects on the renin-angiotensin system. In humans, fetal renal perfusion, which is dependent upon the development of the renin angiotensin system, begins in the second trimester; thus, risk to the fetus increases if COZAVAN is administered during the second or third trimesters of pregnancy.

Neonates with a history of in uterine exposure to COZAVAN

Infants with histories of in-utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria and hyperkalaemia.

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.

Use in Lactation

It is not known whether losartan is excreted in human milk, but studies in rats indicate that both losartan and its active carboxylic acid metabolite are excreted in milk. Many drugs are excreted in human milk and 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 data to suggest that losartan potassium affects the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Losartan potassium has been evaluated for safety in more than 3300 patients treated for essential hypertension and 4058 patients overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with losartan potassium was well tolerated. The overall incidence of adverse experiences reported with losartan potassium was comparable to placebo. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in only 2.3% and 3.7% of patients treated with losartan potassium and placebo, respectively.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as drug-related that occurred with an incidence greater than placebo in one percent or more of patients treated with losartan potassium. In addition, dose-related orthostatic effects were seen in less than one percent of patients. Rarely, rash was reported, although the incidence in controlled clinical trials was less than placebo.

The following table of adverse events is based on four 6-12 week placebo-controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The table includes all adverse events, whether or not attributed to the treatment, occurring in at least 1% of patients treated with losartan and that were more frequent on losartan than placebo.

	Losartan (n=1075) Incidence	Placebo (n=334) Incidence
Digestive		
Diarrhoea	2.4	2.1
Dyspepsia	1.3	1.2
Musculoskeletal		
Cramp, muscle	1.1	0.3
Myalgia	1.0	0.9
Pain, back	1.8	1.2

Pain, leg	1.0	0.0
Nervous system/Psychiatric		
Dizziness	3.5	2.1
Insomnia	1.4	0.6
Respiratory		
Congestion, nasal	2.0	1.2
Cough	3.4	3.3
Infection, upper respiratory	7.9	6.9
Sinus disorder	1.5	1.2
Sinusitis	1.0	0.3

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, oedema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Adverse events occurred at about the same rates in men and women, older and younger patients, and black and non-black patients.

A patient with known hypersensitivity to aspirin and penicillin, when treated with losartan potassium, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued.

Superficial peeling of palms and haemolysis was reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan:

Body as a Whole: facial oedema, fever, orthostatic effects, syncope;

Cardiovascular: angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation;

Digestive: anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting;

Hematologic: anaemia;

Metabolic: gout;

Musculoskeletal: arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness;

Nervous System/Psychiatric: anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paraesthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo;

Respiratory:	dyspnoea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion;
Skin:	alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria;
Special Senses:	blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity;
Urogenital:	impotence, nocturia, urinary frequency, urinary tract infection.

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 purpura, has been reported rarely;

Gastrointestinal: Hepatitis (reported rarely), diarrhoea, liver function abnormalities, vomiting;

General disorders and administration site conditions: malaise;

Haematologic: anaemia, thrombocytopenia (reported rarely);

Musculoskeletal: myalgia, arthralgia;

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers;

Nervous System/Psychiatric: migraine, dysgeusia;

Reproductive system and breast disorders: erectile dysfunction/impotence;

Respiratory: cough;

Skin: urticaria, pruritus, erythroderma, photosensitivity.

Effects on Laboratory Tests

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with losartan potassium alone. No patient discontinued taking losartan potassium alone due to increased BUN or serum creatinine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in Renal Impairment)

Haemoglobin and Haematocrit: Small decreases in haemoglobin and haematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent respectively) occurred frequently in patients treated with losartan potassium alone, but were rarely of clinical importance. No patients were discontinued due to anaemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with losartan potassium alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

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.

Treatment

If symptomatic hypotension should occur, supportive treatment should be instituted. Neither losartan nor the active metabolite can be removed by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Losartan potassium is the first non-peptide orally active angiotensin II receptor (type AT_1) antagonist to be used for the treatment of hypertension. Losartan potassium also provides a reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy and renal protection for type 2 diabetic patients with proteinuria.

Losartan is an oral angiotensin II receptor (type AT_1) antagonist. 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. Based on binding and pharmacological bioassays, losartan binds selectively to the AT_1 receptor. There is also an AT_2 receptor found in many tissues. The functions of AT_2 receptors have not been established. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of synthesis. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

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 increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade.

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 (losartan 1.7%, placebo 1.9%), are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors.

In a study specifically designed to assess the incidence of cough in patients treated with losartan potassium as compared to patients treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan potassium or hydrochlorothiazide was similar and was significantly less than in patients treated with an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical trials in 4131 patients, the incidence of spontaneously reported cough in patients treated with losartan potassium was similar (3.1%) to that of patients treated with placebo (2.6%) or hydrochlorothiazide (4.1%), whereas the incidence with ACE inhibitors was 8.8%.

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. The mechanism of action of the uricosuric effect of losartan studied in normotensive subjects appears to be independent of angiotensin II blockade. Generally, in clinical trials, losartan caused a decrease in serum uric acid (usually 0.4 mg/dL) which was persistent in chronic therapy.

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

Losartan potassium, administered in doses of up to 150 mg once daily, did not cause clinically important changes in fasting triglycerides, total cholesterol in patients with hypertension. The same doses of losartan had no effect on fasting glucose levels.

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive haemodynamic and neurohormonal effects characterised by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and noradrenaline (norepinephrine). The occurrence of hypotension was dose related in these heart failure patients.

The antihypertensive efficacy of losartan potassium was demonstrated in randomised, double-blind, placebo controlled and comparator studies over a 12 week period and in an open-label extension study for over 12 months.

Once-daily administration of losartan potassium to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure; the antihypertensive effect was maintained in clinical studies for up to one year. Measurement of blood pressure at trough (24 hours post-dose) relative to peak (5-6 hours post-dose) demonstrated relatively smooth blood pressure reduction over 24 hours. The antihypertensive effect paralleled the natural diurnal rhythms. Blood pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose. Discontinuation of losartan in hypertensive patients did not result in an abrupt rebound of blood pressure. Despite the significant decrease in blood pressure, administration of losartan potassium has no clinically significant effect on heart rate. The mechanism involved in the lack of reflex tachycardia is not clearly established.

The antihypertensive effect of losartan potassium 50 mg is similar to once-daily administration of enalapril 20 mg. The antihypertensive effect of once-daily administration of losartan potassium 50-100 mg is comparable to once-daily administration of atenolol 50-100 mg. The effect of administration of losartan potassium 50-100 mg once daily also is equivalent to felodipine extended-release 5-10 mg in older hypertensives (> 65 years) after 12 weeks of therapy.

Losartan potassium is equally effective in males and females and in younger (<65 years) and older (>65 years) hypertensives. Plasma concentrations of losartan were about twice as high in female hypertensives as male hypertensives, but concentrations of the active metabolite were similar in males and females. Although losartan potassium is antihypertensive in all races, as with other drugs that affect the renin-angiotensin system, black hypertensive patients have a smaller average response to losartan monotherapy than non black patients. Pharmacokinetic differences due to race have not been studied.

When given together with thiazide-type diuretics, the blood pressure lowering effects of losartan potassium are approximately additive.

Data are currently not available to assess the long-term beneficial effect on morbidity and mortality in patients taking angiotensin II receptor antagonists.

Clinical Trials

LIFE Study

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a large, multicenter, multinational, randomised, triple-blind, active-controlled study conducted in 9193 hypertensive patients aged 55 to 80 years (mean 67 years) with ECG-documented left ventricular hypertrophy. Of the patients enrolled at baseline, 1195 (13%) had diabetes; 1326 (14%), isolated systolic hypertension; 1468 (17%), coronary heart disease; and 728 (8%), cerebrovascular disease. The goal of the study was to demonstrate the cardiovascular protective effects of losartan potassium versus atenolol, over and above the benefits of blood pressure control alone (blood pressure was measured at trough). To meet this objective, the study was designed to achieve equal blood pressure in both treatment groups. Patients were randomised to receive once daily losartan potassium 50mg or atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan potassium or atenolol was then increased to 100 mg once daily. If necessary, other antihypertensive treatments (e.g., increase in dose of hydrochlorothiazide therapy to 25 mg or addition of other diuretic therapy, calcium channel blockers, alpha-blockers, or centrally acting agents, but not ACE inhibitors, angiotensin II antagonists, or beta-blockers) were added to the treatment regimen to reach the goal blood pressure.

In both treatment groups, blood pressure was significantly lowered to similar levels and a similar proportion of patients achieved goal blood pressure. The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. In this trial 5% of the patients treated with losartan potassium suffered stroke compared to 7% of patients treated with atenolol, a reduction of 25% in the relative risk of stroke compared to atenolol (see **Table 1**). The effect of losartan potassium on stroke appeared to be over and above its beneficial effects on blood pressure control alone. The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups. Although the results showed that treatment with losartan potassium resulted in a 13% risk reduction as compared with atenolol for patients reaching the primary composite endpoint, this effect was largely driven by a reduction in the risk on stroke.

TABLE 1 – STROKE RESULTS

Outcome	Losartan potassium (N=4605) n (%)	Rate*	Atenolol (N=4588) n (%)	Rate*	Risk Reduction**	p-value
Stroke	5%	10.8	7%	14.5	25%	0.001

*Per 1000 patient-years of follow up;
**Adjusted for baseline Framingham risk score and ECG measure of LVH

The difference in the incidence of stroke in patients treated with losartan potassium and atenolol amounts to 1 additional stroke prevented for every 53 patients treated with losartan potassium for 5 years. The reduction in the incidence of stroke does not replace the need to adequately titrate patients to adequate blood pressure control.

The effects of losartan potassium versus atenolol on cardiovascular morbidity and mortality were examined in subgroups of patients with a baseline history of diabetes mellitus (n=1195) or isolated systolic hypertension (ISH) (n=1326). For the primary composite endpoint, the results seen in these subgroups were consistent with the benefit of therapy with losartan potassium seen in the overall study population: in diabetic patients, a 24% risk reduction (p=0.03) was observed and in patients with isolated systolic hypertension, a 25% risk reduction (p=0.06) was observed. Consistent with the results seen in the overall population, a reduction in stroke was an important contributor to the benefit observed in patients with diabetes or ISH.

TABLE 2 – STROKE EVENTS WITHIN DEMOGRAPHIC SUBGROUPS

Outcome	Losartan potassium	Rate*	Atenolol n/N (%)	Rate*	Risk Reduction**	p-value

	n/N (%)					
Diabetes	51/586 (8.7%)	19.0	65/609 (10.7%)	24.5	21.2%	0.20
ISH	32/660 (4.8%)	10.6	56/666 (8.4%)	18.9	40.5%	0.020

*Per 1000 patient-years of follow up;
**Adjusted for baseline Framingham risk score and ECG measure of LVH

Race: Based on the LIFE study, the benefits of losartan potassium on cardiovascular morbidity and mortality compared to atenolol do not apply to Black patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in Black patients. In the LIFE study, losartan potassium decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-Black, hypertensive patients with left ventricular hypertrophy (n=8660) as measured by the primary endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction (p=0.003). In this study, however, Black patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with Black patients treated with losartan potassium (p=0.03). In the subgroup of Black patients (n=533; 6% of the LIFE study patients), there were 29 primary endpoints among 263 patients on atenolol (11%, 25.9 per 1000 patient-years) and 46 primary endpoints among 270 patients (17%, 41.8 per 1000 patient-years) on losartan potassium.

RENAAL Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study was a large, multicenter, randomised, placebo-controlled, double-blind study conducted world-wide in 1513 type 2 diabetic patients with proteinuria (assessed by a urinary albumin to creatinine ratio in 2 of 3 morning voids of greater than or equal to 300 mg/g), with or without hypertension. 751 of these patients were treated with losartan potassium. The goal of the study was to demonstrate the renal protective effects of losartan potassium over and above the benefits of blood pressure control alone. To meet this objective the study was designed to achieve equal blood pressure control in both treatment groups. Patients with proteinuria and serum creatinine of 1.3-3.0 mg/dL[2] (115-265 μmol/L) (male patients over 60 kg were only enrolled if serum creatinine was >1.5 mg/dl (>133 μmol/L)) were randomised to receive losartan potassium 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. Other antihypertensive agents (diuretics, calcium-channel blockers, alpha- and beta-blockers, and centrally acting agents) could be added as needed in both groups. 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. For patients reaching the primary composite endpoint the results showed that treatment with losartan potassium as compared with placebo resulted in a reduction in the relative risk of 16.1%. For the following individual and combined components of the primary endpoint, the results also showed significant risk reduction in the group treated with losartan potassium a reduction in the relative risk of 25.3% in doubling of serum creatinine; a reduction in the relative risk of 28.6% in end-stage renal disease; a reduction in the relative risk of 19.9% in end-stage renal disease or death; a reduction in the relative risk of 21.0% in doubling serum creatinine or end-stage renal disease (see **Table 3**).

TABLE 3 - INCIDENCE OF PRIMARY ENDPOINT EVENTS

	Incidence		Risk Reduction	95% C.I.	p-value
	Losartan (n=751)	Placebo (n=762)			
Primary Composite Endpoint	43.5%	47.1%	16.1%	2.3% to 27.9%	0.022
Doubling of Serum Creatinine	21.6%	26.0%	25.3%	7.8% to 39.4%	0.006

ESRD	19.6%	25.5%	28.6%	11.5% to 42.4%	0.002
ESRD or death	255/751 (34.0%)	300/762 (39.4%)	19.9%	5.3% to 32.3%	0.009
Doubling of sCr or ESRD	226/751 (30.1%)	263/762 (34.5%)	21.0%	5.6% to 33.9%	0.010

There was no significant difference observed in the rate of death among patients treated with losartan potassium (21%) compared to those on placebo (20.3%). There was no significant difference observed in the incidence of cardiovascular mortality and morbidity between patients treated with losartan potassium and those who received placebo (p=0.253).

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 (hospitalisation for heart failure, myocardial infarction, revascularisation, stroke, hospitalisation 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 losartan potassium (p<0.001). Treatment with losartan potassium 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.

In this study, losartan potassium was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo.

There was a significant reduction in the mean number of end stage renal disease [ESRD] days with losartan potassium treatment over 3.5 years [33.6 less ESRD days with losartan potassium treatment, (-56.3, -10.9, 95% Confidence Interval)]. It is estimated that one case of ESRD would be prevented for every 16 patients that are treated with losartan potassium over a 3.5 year period.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The active carboxylic metabolite (losartan acid) is responsible for most of the angiotensin II receptor antagonism.

The systemic bioavailability of losartan film-coated tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in approximately 1 hour and 4 hours, respectively. While maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 6 times as great as that of losartan. Food slows the absorption of losartan and leads to slightly decreased levels of losartan (AUC about 18% decreased) and the active metabolite (AUC about 13% decreased). However, in each case the changes were small and there was no clinically significant effect on the plasma concentration profile of losartan.

A separate bioavailability study was conducted comparing generic losartan potassium 50 mg tablets with the innovator losartan potassium 50 mg tablets. The generic and innovator mean C_{max} values for the active carboxylic metabolite were 403.051 ng/mL and 399.633 ng/mL, respectively. The point estimate of the generic to innovator ratio of the geometric means for C_{max} was 1.0231 with a 90% confidence interval of [0.9813, 1.0668]. The generic and innovator mean AUC_{∞} values for the active carboxylic metabolite were 3167.94 ng*hr/mL and 3090.24 ng*hr/mL, respectively. The point estimate of the generic to innovator ratio of the geometric means for AUC_{∞} was 1.0314 with a 90% confidence interval of [1.0069, 1.0565]. The T_{max} for both the generic and innovator tablets was 4 hours.

Distribution

Both losartan and its active metabolite are >99% 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.

The volume of distribution of losartan is about 34 litres and of the active metabolite is about 12 litres.

Metabolism

Losartan undergoes substantial first-pass metabolism by cytochrome P450.

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-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. 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.

Excretion

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.

Following oral administration, plasma concentrations of losartan and its active metabolites decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

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

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in haemodialysis patients.

Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in haemodialysis patients. No dosage adjustment is necessary for patients with renal impairment unless they are volume depleted.

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 haemodialysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of genotoxic activity was observed in assays for DNA damage, gene mutations and chromosomal damage.

Carcinogenicity

In animal studies, there was no evidence of carcinogenic activity when losartan potassium was administered orally to mice at doses up to 200 mg/kg/day for 92 weeks, or to rats at doses up to 270 mg/kg/day for 105 weeks.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each COZAVAN film-coated tablet contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, pregelatinised maize starch, magnesium stearate, Opadry complete film coating system 20A58900 White (ARTG PI No: 13043).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVDC/PE/PVC/Aluminium blisters

25 mg tablets: Available in blister packs containing 10 (starter pack), 30 or 60 tablets.

50 mg tablets: Available in blister packs containing 10 (starter pack) or 30 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 156235 - COZAVAN losartan potassium 25 mg film-coated tablet blister pack

AUST R 156234 - COZAVAN losartan potassium 50 mg film-coated tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

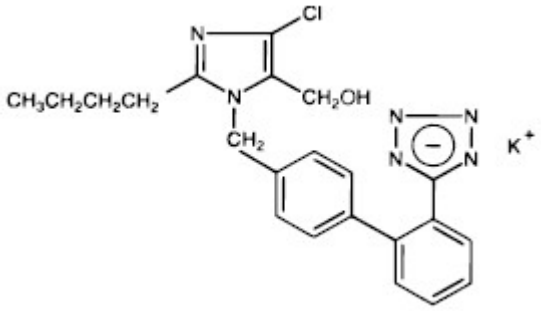
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Losartan potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol monopotassium salt.

Oxidation of the 5-hydroxymethyl group on the imidazole ring results in the active metabolite of losartan.

Chemical Structure



Molecular formula:	$C_{22}H_{22}ClKN_6O$
Molecular weight:	461.01

CAS Number

124750-99-8

Losartan potassium is a white to off-white free-flowing crystalline powder. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

28/06/2010

10 DATE OF REVISION

19/05/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes:
6.5	Minor editorial changes

8	Update sponsor’s details

COZAVAN® is a Viatris company trade mark

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