

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

LOSARTAN ACTAVIS (Losartan Potassium 12.5mg, 25mg, 50mg and 100mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

12.5 mg losartan potassium

25 mg losartan potassium

50 mg losartan potassium

100mg losartan potassium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablets

12.5 mg tablet: Blue, oval, biconvex film coated tablets, plain on both sides

Dimensions: 8.2mm x 4.4 mm

25 mg tablet: White to off white, oval shaped, biconvex, film coated tablets with '25' debossing on one side and plain on the other side.

Dimensions: 8.2 x 4.4 mm

50 mg tablet: White to off white, oval shaped, biconvex, film coated tablets with '50' debossing on one side and plain on the other side.

Dimensions: 10.3 x 5.5 mm

100 mg tablet: White to off white, almond shaped, biconvex, film coated tablets with '100' debossing on one side and plain on the other side.

Dimensions: 11.7x7.2mm

Do not halve the tablets. Dose equivalence when the tablet is divided has not been established.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

LOSARTAN ACTAVIS is indicated for the treatment of hypertension.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

LOSARTAN ACTAVIS is indicated to reduce the risk of cardiovascular morbidity and mortality as measured by the combined incidence of cardiovascular death, stroke, and myocardial infarction in hypertensive patients with left ventricular hypertrophy (see 4.4 Special warnings and precautions for use, Race).

Heart Failure

LOSARTAN ACTAVIS is indicated for the treatment of heart failure in patients who cannot tolerate an ACE inhibitor. Switching patients with heart failure who are stable on an ACE inhibitor to Losartan Potassium is not recommended.

Renal Protection in Type 2 Diabetic Patients with Proteinuria

LOSARTAN ACTAVIS is indicated to delay the progression of renal disease as measured by a reduction in the combined incidence of doubling of serum creatinine, end stage renal disease (need for dialysis or renal transplantation) or death; and to reduce proteinuria.

4.2 Dose and method of administration

Dose

Hypertension

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. Some patients may receive an additional benefit by increasing the dose 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 4.4 Special warnings and precautions for use).

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 4.4 Special warnings and precautions for use).

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of LOSARTAN ACTAVIS once daily. A low dose of hydrochlorothiazide should be added and/or the dose of LOSARTAN ACTAVIS should be increased to 100 mg once daily based on blood pressure response.

Heart Failure

The initial dose of LOSARTAN ACTAVIS in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily and 50 mg daily) to the usual maintenance dose of 50 mg once daily, as tolerated by the patient.

LOSARTAN ACTAVIS is usually given in combination with diuretics and digitalis.

Renal Protection in Type 2 Diabetic Patients with 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. LOSARTAN ACTAVIS 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).

Method of administration

LOSARTAN ACTAVIS may be administered with or without food.

LOSARTAN ACTAVIS may be administered with or without other antihypertensive agents.

4.3 Contraindications

LOSARTAN ACTAVIS is contraindicated in patients who are hypersensitive to any component of this product.

LOSARTAN ACTAVIS is contraindicated during the 2nd and 3rd trimester of pregnancy (see 4.4 Special warnings and precautions for use).

LOSARTAN ACTAVIS is contraindicated in patients with severe hepatic impairment.

LOSARTAN ACTAVIS should not be administered with aliskiren in patients with diabetes (see 4.5 Interaction with other medicines and other forms of interaction).

4.4 Special warnings and precautions for use

Foetal Toxicity

Use of drugs 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 LOSARTAN ACTAVIS as soon as possible (see 4.6 Fertility, pregnancy and lactation).

Hypersensitivity

Angioedema (see 4.8 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 LOSARTAN ACTAVIS, or a lower starting dose should be used (see 4.2 Dose and method of administration). In type 2 diabetic patients with nephropathy treated with an angiotensin II antagonist, serum potassium levels should be monitored.

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 losartan potassium as compared to the placebo group; however, few patients discontinued therapy due to hyperkalaemia (see 4.8 Undesirable effects, *Laboratory Test Findings*).

Liver Function 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. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment (see 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

Renal Function Impairment

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported in susceptible individuals; these changes in renal function may be reversible upon discontinuation of therapy.

Other medicines 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; these changes in renal function may be reversible upon discontinuation of therapy.

Use in the Elderly

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

Race

Based on the LIFE (Losartan Intervention For Endpoint reduction in hypertension) 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 overall LIFE study population (n=9193), treatment with losartan potassium resulted in a 13.0% risk reduction (p=0.021) as compared to atenolol for patients reaching the primary composite endpoint of the combined incidence of cardiovascular death, stroke, and myocardial infarction. In this 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.

Dual blockade of the renin-angiotensin-aldosterone system

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 losartan potassium and other agents that affect the RAAS. Do not coadminister aliskiren with losartan potassium in patients with diabetes. Avoid use of aliskiren with losartan potassium in patients with renal impairment (GFR <60 ml/min).

4.5 Interaction with other medicines and other forms of interaction

In clinical pharmacokinetic trials, no medicine interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital and 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.

As with other medicines that block angiotensin II or its effect, concomitant use of 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 medicines 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 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. These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

4.6 Fertility, pregnancy and lactation

Pregnancy

When used in pregnancy during the second and third trimesters, medicines that act directly on the renin-angiotensin system can cause injury and death to the developing foetus. When pregnancy is detected, LOSARTAN ACTAVIS should be discontinued as soon as possible.

Although there is no experience with the use of LOSARTAN ACTAVIS 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 LOSARTAN ACTAVIS is administered during the second or third trimester of pregnancy.

Use of drugs 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 LOSARTAN ACTAVIS 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 foetal 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 foetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the foetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue LOSARTAN ACTAVIS, unless it is considered life-saving for the mother. Foetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the foetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to LOSARTAN ACTAVIS for hypotension, oliguria, and hyperkalaemia.

Nursing Mothers

It is not known whether losartan is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for adverse effects on the nursing infant, LOSARTAN ACTAVIS is not recommended in nursing mothers and alternative treatments with better established safety profiles during breast feeding are preferable.

Paediatric Use

Antihypertensive effects of losartan potassium have been established in hypertensive paediatric patients aged > 1 month to 16 years. Use of losartan potassium in these age groups is supported by evidence from adequate and well-controlled studies of losartan potassium in paediatric and adult patients as well as by literature in paediatric patients.

The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/kg of losartan (mean doses). The active metabolite is formed from losartan in all age groups. Pharmacokinetics of losartan and its active metabolite are generally similar across the studied age groups and consistent with pharmacokinetic historic data in adults.

In a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age, patients who weighed ≥ 20 kg to <50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed

≥ 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, losartan potassium was generally well tolerated.

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients ≥ 20 to <50 kg. The dose can be increased to a maximum of 50 mg once daily. In patients ≥ 50 kg, the starting dose is 50 mg once daily. The dose can be increased to a maximum of 100 mg once daily.

In paediatric patients who are intravascularly volume depleted, these conditions should be corrected prior to administration of LOSARTAN ACTAVIS.

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

LOSARTAN ACTAVIS is not recommended in paediatric patients with glomerular filtration rate <30 mL/min/1.73 m², in paediatric patients with hepatic impairment, or in neonates as no data are available.

Neonates with a history of *in utero* exposure to losartan potassium:

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Losartan potassium has been evaluated for safety in more than 2500 patients treated for essential hypertension. 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 effect reported as medicine-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.

In these double-blind controlled clinical trials, for essential hypertension the following adverse experiences reported with losartan potassium occurred in ≥1 percent of patients, regardless of medicine relationship:

	losartan-potassium (n=2085)	Placebo (n=535)
<i>Body as a Whole</i>		
Abdominal pain	1.7	1.7
Asthenia/fatigue	3.8	3.9
Chest pain	1.1	2.6
Oedema/swelling	1.7	1.9

	losartan-potassium (n=2085)	Placebo (n=535)
<i>Cardiovascular</i>		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
<i>Digestive</i>		
Diarrhoea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
<i>Musculoskeletal</i>		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
<i>Nervous/Psychiatric</i>		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
<i>Respiratory</i>		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

Losartan potassium was generally well tolerated in a controlled clinical trial in hypertensive patients with left ventricular hypertrophy. The most common drug-related side effects were dizziness, asthenia/fatigue, and vertigo.

In the HEAAL (Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan) study the clinically important medicine related adverse effects that occurred more frequently in patients receiving losartan potassium 150mg than in patients receiving Losartan potassium 50mg were hyperkalaemia, renal impairment, renal failure, hypotension and increases in blood creatinine, blood potassium and blood urea. These adverse effects did not lead to significantly more treatment discontinuations in the patients receiving losartan potassium 150 mg

In the LIFE study, among patients without diabetes at baseline, there was a lower incidence of new onset diabetes mellitus with losartan potassium as compared to atenolol (242 patients versus 320 patients, respectively, $p < 0.001$). Because there was no placebo group included in the study, it is not known if this represents a beneficial effect of losartan Potassium or an adverse effect of atenolol.

Losartan potassium was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria. The most common drug-related side effects were asthenia/fatigue, dizziness,

hypotension and hyperkalaemia (see 4.4 Special warnings and precautions for use, *Hypotension and Electrolyte/Fluid Imbalance*.)

Losartan potassium was generally well tolerated in controlled clinical trials for heart failure. Adverse experiences observed were typical of those expected in this population. The most common medicine-related side effects were dizziness and hypotension.

The following additional 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 medicines including ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely.

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

General disorders and administration site conditions: Malaise

Haematologic: Anaemia thrombocytopenia (reported rarely)

Musculoskeletal: Myalgia, arthralgia.

Nervous System/Psychiatric: Migraine, dysgeusia.

Respiratory: Cough

Skin: Urticaria, pruritus, erythroderma, photosensitivity

Reproductive system and breast disorders: Erectile dysfunction/impotence

Metabolism and nutritional disorder: Hyponatraemia

Laboratory Test Findings

In controlled clinical trials for essential hypertension, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan potassium. Hyperkalaemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients in the hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with proteinuria, 9.9% of patients treated with losartan potassium and 3.4% of patients treated with placebo developed hyperkalemia (see 4.4 Special warnings and precautions for use). Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy.

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. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg (3000 mg/m²) and 2000 mg/kg (11,800 mg/m²), respectively.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by haemodialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonist, ATC Code: C09CA01

LOSARTAN ACTAVIS (losartan potassium), the first of a new class of agents for the treatment of hypertension is an angiotensin II receptor (type AT₁) antagonist. It also provides a reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy and renal protection for type 2 diabetic patients with proteinuria.

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 AT₁ 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. A second angiotensin II receptor has been identified as the AT₂ receptor subtype, but it plays no known role in cardiovascular homeostasis.

Losartan is a potent, synthetic, orally active compound. Based on binding and pharmacological bioassays, it binds selectively to the AT₁ receptor. *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. In contrast to some peptide antagonists of angiotensin II, losartan has no agonist effects.

Losartan binds selectively to the AT₁ 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 AT₁ 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.

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 systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the medicine was administered with a standardised meal.

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.

Metabolism

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ¹⁴C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. 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.

Elimination

Plasma clearance of losartan and its active metabolite is about 600mL/min and 50mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74mL/min and 26mL/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 200mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. 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 ¹⁴C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces. Following an intravenous dose of ¹⁴C-labelled losartan in man, about 43% of radioactivity is recovered in the urine and 50% in the faeces.

Characteristics in Patients

The plasma concentrations of losartan and its active metabolite observed in elderly male hypertensives are not significantly different from those observed in young male hypertensives.

Plasma concentrations of losartan were up to 2-fold higher in female hypertensives as compared to male hypertensives. Concentrations of the active metabolite were not different in males and females. This apparent pharmacokinetic difference is not judged to be of clinical significance.

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 10mL/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.

5.3 Preclinical safety data

Animal Toxicology/Carcinogenesis

Losartan potassium was not carcinogenic when administered at maximum tolerated dosage levels to rats and mice for 105 and 92 weeks, respectively. These maximum tolerated dosage levels provided respective margins of systemic exposure for losartan and its pharmacologically active metabolite over that achieved in humans treated with 50 mg of losartan of approximately 270- and 150-fold in rats and 45- and 27-fold in mice.

Mutagenesis

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution and *in vitro* chromosomal aberration assays at concentrations that were approximately 1700 times greater than the maximum plasma level achieved in man at the recommended therapeutic dosage level. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of toxic oral doses of up to 1500 mg/kg (4500 mg/m²) (750 times the maximum recommended daily human dose).

In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Reproduction

Fertility and reproductive performance were not affected in studies with male and female rats given oral doses of losartan potassium up to approximately 150 and 300 mg/kg/day, respectively. These dosages provide respective margins of systemic exposure for losartan and its pharmacologically active metabolite of approximately 150/125-fold in male rats and 300/170-fold in female rats over that achieved in man at the recommended daily dose.

Development

Losartan potassium has been shown to produce adverse effects in rat foetuses and neonates. The effects include decreased body weight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to medicine exposure in late gestation and during lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains the following inactive ingredients: maize starch, microcrystalline cellulose, purified talc, colloidal silicon dioxide, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, macrogol 6000, indigo carmine (12.5mg only), purified water.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

LOSARTAN ACTAVIS 12.5 mg film coated tablets: Blister packs containing 14, 28, 56 and 84 tablets.

LOSARTAN ACTAVIS 25 mg film coated tablets are available in packs of 28, 56 and 84 tablets.

LOSARTAN ACTAVIS 50 mg film coated tablets are available in packs of 28, 56 and 84 tablets.

LOSARTAN ACTAVIS 100 mg film coated tablets are available in packs of 28, 56 and 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited

PO Box 128 244

Remuera

Auckland 1541

Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

Losartan Actavis 25 mg, 50 mg, 100 mg: 7/04/2011

Losartan Actavis 12.5 mg: 18/10/2012

10. DATE OF REVISION OF THE TEXT

12 April 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
3.	Amend terminology for tablet appearance for the 25 mg, 50 mg and 100 mg tablet strengths.