NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Arrow-Losartan potassium & Hydrochlorothiazide, film-coated tablets 50 mg/12.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains losartan potassium 50 mg and hydrochlorothiazide 12.5 mg.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Yellow coloured, oval shaped, biconvex, film-coated tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension
Arrow-Losartan potassium and Hydrochlorothiazide is indicated for the treatment of hypertension, for patients in whom combination therapy is appropriate.

Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy
Arrow-Losartan potassium and Hydrochlorothiazide is a combination of losartan and hydrochlorothiazide. In patients with hypertension and left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, reduces 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 section 4.4 Special Warnings and Precautions for Use, *Race*).

4.2 Dose and method of administration
Dose
Hypertension
The usual starting and maintenance dose of Arrow-Losartan potassium and Hydrochlorothiazide is one tablet once daily. For patients who do not respond adequately to one tablet, the dosage may be increased to two tablets once daily. The maximum dose is two tablets once daily. In general the antihypertensive effect is attained within three weeks after initiation of therapy.

Arrow-Losartan potassium and Hydrochlorothiazide should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).

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 once daily. If goal blood pressure is not reached with losartan 50 mg, therapy should be titrated using a combination of losartan and a low dose of hydrochlorothiazide (12.5 mg*) and, if needed, the dose should then be increased to losartan 100 mg and hydrochlorothiazide 12.5 mg once daily. If necessary, the dose should be increased to losartan 100 mg and hydrochlorothiazide 25 mg once daily. Arrow-Losartan potassium and Hydrochlorothiazide is a suitable alternative formulation in patients who would otherwise be treated concomitantly with losartan plus hydrochlorothiazide.

*Note: Hydrochlorothiazide is not available in New Zealand.

Special Populations

Renal impairment and haemodialysis patients

No initial dosage adjustment is necessary in patients with moderate renal impairment (ie. creatinine clearance 30-50 mL/min). Arrow-Losartan potassium and Hydrochlorothiazide is not recommended for haemodialysis patients. Arrow-Losartan potassium and Hydrochlorothiazide must not be used in patients with severe renal impairment (ie. creatinine clearance ≤ 30mL/min)(see section 4.3 Contraindications).

Hepatic impairment

Arrow-Losartan potassium and Hydrochlorothiazide is contraindicated in patients with hepatic impairment (see section 4.3 Contraindications).

Use in patients with intravascular volume depletion

Volume and/or sodium depletion should be corrected prior to administration of this medicine.

Elderly

No initial dosage adjustment of Arrow-Losartan potassium and Hydrochlorothiazide is necessary for elderly patients.

Paediatric population

Arrow-Losartan potassium and Hydrochlorothiazide is not recommended for use in children and adolescents under 18 years of age due to insufficient data on safety and efficacy.

Method of administration

Arrow-Losartan potassium and Hydrochlorothiazide may be administered with other antihypertensive agents.

Arrow-Losartan potassium and Hydrochlorothiazide may be administered with or without food.

4.3 Contraindications

Arrow-Losartan potassium and Hydrochlorothiazide is contraindicated in:

- Patients who are hypersensitive to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any component of this product
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- 2nd and 3rd trimester of pregnancy (see section 4.4 Special warnings and precautions for use and section 4.6 Fertility, pregnancy and lactation)
- Severe renal impairment (i.e. creatinine clearance < 30 ml/min)
- Patients with anuria
- Arrow Losartan potassium and hydrochlorothiazide should not be administered with aliskiren in patients with diabetes or renal impairment (GFR < 60 ml/min/1.73 m^2) (see section 4.5 Interaction with other medicines and other forms of interaction)

4.4 Special warnings and precautions for use

Losartan

Angioedema

Patients with a history of angioedema (swelling of the face, lips, throat and/or tongue) should be closely monitored (see section 4.8 Undesirable effects).

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

Hypotension and intravascular volume depletion
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of this medicine product (see sections 4.2 Dose and method of administration and 4.3 Contraindications).

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30-50 mL/min should be closely monitored.

The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with this medicine is not recommended (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Liver function impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, this medicine should be used with caution in patients with a history of mild to moderate hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore this medicine is contraindicated in patients with severe hepatic impairment (see sections 4.2 Dose and method of administration and 4.3 Contraindications and section 5.2 Pharmacodynamic kinetics).

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this medicine is not recommended.

Coronary heart disease and cerebrovascular disease
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in African, African/American people than in non-African, African/American, possibly because of higher prevalence of low-renin states in the African, African/American hypertensive population.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see section 4.5 Interaction with other medicinal products and other forms of interaction and section 5.1 Pharmacodynamic properties).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments, which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see section 4.3 Contraindications and section 4.6 Fertility, pregnancy and lactation).

Hydrochlorothiazide

Acute Respiratory Distress Syndrome (ARDS)
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Arrow-Losartan potassium and Hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Hypotension and electrolyte/fluid imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see section 4.5 Interaction with other medicines and other forms of interaction). Latent diabetes mellitus may manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

This medicine is contraindicated for patients with severe hepatic impairment (see section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties).

Non-melanoma skin cancer
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry.

Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventative measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8 Undesirable effects).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Pregnancy
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Hydrochlorothiazide should not be used for essential hypertension in pregnant women, except in rare situations where no other alternative treatment could be used (see section 4.3 Contraindications and section 4.6 Fertility, pregnancy and lactation).

When used in pregnancy during the second and third trimesters, medicines that act directly on the renin-angiotensin system can cause injury and even death in the developing foetus. When pregnancy is

detected, a combination of losartan potassium 50 mg/ hydrochlorothiazide 12.5 mg tablet should be discontinued as soon as possible. (see section 4.6 Fertility, pregnancy and lactation for more details)

Paediatric Use
Safety and effectiveness in children have not been established.

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

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.

Other
In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Lactose
Arrow-Losartan potassium & Hydrochlorothiazide contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in the Elderly
In clinical studies there were no clinically significant differences in the efficacy or safety profiles of a combination of losartan potassium 50 mg/hydrochlorothiazide 12.5 mg in older (≥ 65 years) and younger (<65 years) patients.

4.5 Interaction with other medicines and other forms of interaction

Losartan
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 effects, 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. Co-medication is not advisable.

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.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses) and non-selective NSAIDs, attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofen, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side effect, may increase the risk of hypotension.

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

Hydrochlorothiazide
When given concurrently the following medicines may interact with thiazide diuretics:

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

Antidiabetic medicines (oral agents and insulin): treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicine may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive medicines: additive effect.

Cholestyramine and colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH or glycyrrhizin (found in liquorice): intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g. adrenaline): possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarising (e.g. tubocurarine): possible increased responsiveness to the muscle relaxant.

Lithium: Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended. Refer to the package insert for lithium preparations before use of such preparations.

Medicines used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol): Dosage adjustment of uricosuric medicines may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden): Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate): Thiazides may reduce the renal excretion of cytotoxic medicines and potentiate their myelosuppressive effects.

Salicylates: In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa: There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Ciclosporin: Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicines affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when this medicine is administered with medicines affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following Torsade de pointes (ventricular tachycardia) - inducing medicines (including some antiarrhythmics), hypokalaemia being a predisposing factor to Torsade de pointes (ventricular tachycardia):

- Class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts: Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Laboratory test interactions: Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4 Special warnings and precautions for use).

Carbamazepine: Risk of symptomatic hyponatraemia. Clinical and biological monitoring is required.

Iodine contrast media: In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

Amphotericin B (parenteral), corticosteroids, ACTH, stimulant laxatives, or glycyrrhizin (found in liquorice): Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

Non-steroidal anti-inflammatory medicines: Including Cyclooxygenase-2 Inhibitors: In some patients, the administration of a non-steroidal anti-inflammatory agent including a selective cyclooxygenase-2 inhibitor can reduce the diuretic, natriuretic, and antihypertensive effects of diuretics.

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

Medicine/Laboratory Test Interactions
Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs)

The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4 Special warnings and precautions for use). The use of AIIRAs is contraindicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however. a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments, which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3 Preclinical safety data). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see section 4.4 Contraindications and section 4.4 Special warnings and precautions for use).

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women, except in rare situations where no other alternative treatment could be used.

Breastfeeding

AIIRAs

Because no information is available regarding the use of this medicine during breastfeeding, this medicine is not recommended and alternative treatments with better-established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of this medicine during breastfeeding is not recommended. If this medicine is used during breastfeeding, doses should be kept as low as possible.

Fertility

Losartan-Hydrochlorothiazide

Losartan potassium-hydrochlorothiazide administration had no effect on the reproductive performance or fertility in male rats at dosage levels of up to 135 mg/kg/day of losartan in combination with 33.75 mg/kg/day of hydrochlorothiazide. These dosage levels provided respective plasma concentrations (AUC) for losartan, the active metabolite and hydrochlorothiazide that were approximately 260-, 120- and 50- fold greater than those achieved in man with 50 mg of losartan potassium in combination with 12.5 mg hydrochlorothiazide. In female rats, however, the co-administration of losartan potassium/hydrochlorothiazide (10/2.5 mg/kg/day) induced a slight but statistically significant decrease in fecundity and fertility indices. Compared to plasma concentrations in man (see above) these dosage levels provided respective increases in plasma concentration (AUC) for losartan, the active metabolite, and hydrochlorothiazide of approximately 15-, 4-, and 5-fold.

Losartan

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.

Hydrochlorothiazide

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

4.7 Effects on ability to drive and use machines

There are no data to suggest that Arrow-Losartan Potassium and Hydrochlorothiazide 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 Undesirable effects).

4.8 Undesirable effects

Summary of the safety profile

In clinical trials with losartan and hydrochlorothiazide, no adverse reactions peculiar to this combination of substances were observed. The adverse reactions were restricted to those which were formerly observed with losartan potassium salt and/or hydrochlorothiazide.

List of adverse reactions

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

In controlled clinical trials for essential hypertension, dizziness was the only adverse reaction reported as substance-related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan and hydrochlorothiazide.

Next to these effects, there are further adverse reactions reported after the introduction of the product to the market as follows:

Metabolism and nutrition disorders	
Rare:	Hyperkalaemia
Hepatobiliary disorders	
Rare:	Hepatitis
Investigations	
Rare	Alanine aminotransferase increased

Additional adverse reactions that have been seen with one of the individual components and may be potential adverse reactions with losartan or hydrochlorothiazide are the following:

Losartan

Infections and infestations	
Common:	Upper respiratory tract infection, sinusitis
Uncommon:	Conjunctivitis, pharyngitis, laryngitis, bronchitis, rhinitis, urinary tract infection
Blood and lymphatic system disorders	
Uncommon	Anaemia, haemolysis
Immune system disorders	
Rare	Anaphylactic reaction
Metabolism and nutrition disorders	
Common	Hyperkalaemia
Uncommon	Decreased appetite, gout
Psychiatric disorders	
Common	Insomnia
Uncommon	Anxiety, anxiety disorder, panic disorder, confusional state, depression, abnormal dreams, sleep disorder, nervousness, libido decreased
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Paraesthesia, neuropathy peripheral, tremor, migraine, syncope, somnolence, memory impairment, cerebrovascular accident, nervousness
Not known	Dysgeusia
Eye disorders	
Uncommon	Vision blurred, eye irritation, eyelid pain, visual acuity reduced
Ear and labyrinth disorders	
Uncommon	Vertigo, tinnitus
Cardiac disorders	
Uncommon	Angina pectoris, atrioventricular block second degree, myocardial infarction, palpitations, arrhythmia, atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation
Vascular disorders	
Uncommon	Vasculitis, hypotension, orthostatic hypotension, flushing
Not known	Dose-related orthostatic effects
Respiratory, thoracic and mediastinal disorders	
Common	Cough, nasal congestion, sinus disorder
Uncommon	Oropharyngeal discomfort, dyspnoea, epistaxis, respiratory tract congestion

Gastrointestinal disorders

Common	Abdominal pain, nausea, diarrhoea, dyspepsia
Uncommon	Constipation, toothache, dry mouth, flatulence, gastritis, vomiting
Rare	Intestinal angioedema

Hepatobiliary disorders

Not known	Hepatic function abnormal

Skin and subcutaneous tissue disorders

Uncommon	Alopecia, dermatitis, dry skin, erythema, photosensitivity reaction, pruritus, rash, urticaria, hyperhidrosis, Henoch-Schonlein purpura, ecchymosis
Rare	Angioedema

Musculoskeletal and connective tissue disorders

Common	Muscle spasm, back pain, leg pain, myalgia
Uncommon	Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, musculoskeletal stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, musclar weakness
Not known	Rhabdomyolysis

Renal and urinary disorders

Uncommon	Nocturia, pollakiuria

Reproductive system and breast disorders

Uncommon	Erectile dysfunction

General disorders and administration site conditions

Common	Asthenia, fatigue, chest pain
Uncommon	Face oedema, pyrexia,

Investigations

Common	Haematocrit decreased, haemoglobin decreased
Uncommon	Blood urea increased, blood creatinine increased
Very rare	Hepatic enzyme increased , blood bilirubin increased

Hydrochlorothiazide

Infections and infestations

Uncommon	Sialoadenitis

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Not known	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)

Blood and lymphatic system disorders

Uncommon	Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, thrombocytopenia

Immune system disorders

Rare	Anaphylactic reaction

Metabolism and nutrition disorders

Uncommon	Decreased appetite, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Psychiatric disorders	
Uncommon	Insomnia
Nervous system disorders	
Common	Headache
Uncommon	Dizziness
Eye disorders	
Uncommon	Vision blurred, xanthopsia
Not known	Choroidal effusion
Vascular disorders	
Uncommon	Vasculitis necrotizing, vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Respiratory distress, pneumonitis, pulmonary oedema
Very rare	Acute respiratory distress syndrome (ARDS)
Gastrointestinal disorders	
Uncommon	Abdominal rigidity, epigastric discomfort, nausea, vomiting, diarrhoea, constipation, pancreatitis
Hepatobiliary disorders	
Uncommon	Jaundice, cholestasis
Skin and subcutaneous tissue disorders	
Uncommon	Photosensitivity reaction, urticaria, toxic epidermal necrolysis, purpura, cutaneous vasculitis
Not known	Cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle spasms
Renal and urinary disorders	
Uncommon	Glycosuria, tubulointerstitial nephritis, renal impairment, renal failure
General disorders and administration site conditions	
Uncommon	Pyrexia

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of losartan - hydrochlorothiazide. Hyperkalaemia (serum potassium >5.5 mEq/L) occurred in 0.7% of patients, but in these trials, discontinuation of a combination of losartan - hydrochlorothiazide due to hyperkalaemia was not necessary. 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://pophealth.my.site.com/carmreportnz/s

4.9 Overdose
Losartan potassium
No specific information is available on the treatment of overdosage with losartan potassium 50 mg/hydrochlorothiazide 12.5 mg tablet. Treatment is symptomatic and supportive. Therapy with Arrow-Losartan potassium and Hydrochlorothiazide should be discontinued and the patient observed closely. Suggested measures include induction of emesis if ingestion is recent, and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

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

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

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrythmias.

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

For risk assessment and 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: Agents acting on the renin-angiotensin system; Angiotensin II antagonists, Combinations; Angiotensin II antagonists and diuretics, ATC code: C09DA01.

Losartan - Hydrochlorothiazide
The components of a combination of losartan potassium 50 mg/hydrochlorothiazide 12.5 mg have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricemia.

Losartan and hydrochlorothiazide, when used in combination are additive in their antihypertensive efficacy.

The antihypertensive effect of a combination of losartan potassium 50mg / hydrochlorothiazide 12.5 mg is sustained for a 24-hour period. In clinical studies of at least one year's duration, the

antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of a combination of losartan potassium 50 mg/ hydrochlorothiazide 12.5 mg had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with a combination of losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

In a study comparing a combination of losartan 50 mg/hydrochlorothiazide 12.5 mg with the combination captopril 50 mg/hydrochlorothiazide 25 mg in young (<65 years) and elderly (≥65 years) hypertensive patients, the antihypertensive responses were similar between the two treatments and by age groups. Overall, there were statistically significantly fewer drug-related clinical adverse experiences and discontinuations due to clinical adverse events with a combination of losartan 50 mg/hydrochlorothiazide 12.5 mg than with captopril 50mg/hydrochlorothiazide 25 mg.

A study with 131 patients with severe hypertension showed the utility of a combination of losartan potassium 50 mg/hydrochlorothiazide 12.5 mg administered as initial therapy and in a regimen with other antihypertensive agents after 12 weeks of therapy.

A combination of losartan potassium 50 mg/hydrochlorothiazide 12.5 mg is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (≥ 65 years) patients and is effective in all degrees of hypertension.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

Race

Based on the LIFE (Losartan Intervention for Endpoint reduction in hypertension) study, the benefits of losartan on cardiovascular morbidity and mortality compared to atenolol do not apply to African, African/American patients with hypertension and left ventricular hypertrophy although both treatment regimens effectively lowered blood pressure in African, African/American patients. In the overall LIFE study population (n=9193), treatment with losartan 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 decreased the risk of cardiovascular morbidity and mortality compared to atenolol in non-African, African/American, 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, African, African/American patients treated with atenolol were at lower risk of experiencing the primary composite endpoint compared with African, African/American patients treated with losartan (p=0.03). In the subgroup of African, African/American 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.

5.2 Pharmacokinetic properties

Absorption

Losartan

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 drug was administered with a standardized meal.

Losartan-Hydrochlorothiazide

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

Distribution

Losartan

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.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Biotransformation

Losartan

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. 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

Losartan

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 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 ^{14}C-labelled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

Hepatic Impairment

Losartan

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

Carcinogenesis

Losartan

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.

Hydrochlorothiazide

Two-year feeding studies in mice and rats uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The studies, however, uncovered equivocal evidence for hepato carcinogenicity in male mice.

Mutagenesis

Losartan-Hydrochlorothiazide

Losartan potassium-hydrochlorothiazide was negative in the Ames microbial mutagenesis assay and the V-79 Chinese hamster lung cell mutagenesis assay. In addition, there was no evidence of direct genotoxicity in the *in vitro* alkaline elution assay in rat hepatocytes and in vitro chromosomal aberration assay in Chinese hamster ovary cells at noncytotoxic concentrations.

Losartan

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.

Hydrochlorothiazide

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 μg/ml, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Development

Losartan-Hydrochlorothiazide

There was no evidence of teratogenicity in rats or rabbits treated with losartan potassium-hydrochlorothiazide. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including decreased body weight and renal toxicity, also occurred when pregnant rats were treated with losartan potassium-hydrochlorothiazide during late gestation and/or lactation.

Losartan

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 drug exposure in late gestation and during lactation.

Hydrochlorothiazide

Reproduction studies in the rabbit, the mouse and the rat at doses up to 100 mg/kg/day (50 times the maximum human dose) showed no evidence of external abnormalities of the foetus due to hydrochlorothiazide. Hydrochlorothiazide given in a two-litter study in rats at doses of 4-5.6 mg/kg/day (approximately 2-3 times the maximum recommended human dose) did not impair fertility or produce birth abnormalities in the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose (Avicel PH 101), pregelatinized starch, maize starch (Dried), colloidal anhydrous silica, magnesium stearate, hydroxy propyl methyl cellulose 15cps, titanium dioxide, purified talc, Macrogol 6000, Quinoline yellow lake and purified water.

Each tablet contains 4.24 mg of potassium.

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C. Store in the original package.

6.5 Nature and contents of container

Single blister of 10 or 14 tablets each.

Blister pack of 10, 20, 30, 50, 60, 80, 90 or 100 tablets packed in an outer carton (for 10’s blister) and 14, 28, 56, 84 or 98 tablets packed in an outer carton (for 14’s blister)

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

26 May 2011

10. DATE OF REVISION OF THE TEXT

30 April 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4, 4.8	Update to include intestinal angioedema Added title for ethnic differences; update paragraph for hydrochlorothiazide and the antidiabetic medicines
4.8	Update to URL for reporting suspected adverse reactions
4.9	Added risk assessment wording
5.1	Race paragraph moved from section 4.4.