

# 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 and Hepatic Impairment*

Arrow-Losartan potassium and Hydrochlorothiazide is not recommended for patients with severe renal impairment (creatinine clearance  $\leq$  30mL/min) or for patients with hepatic impairment.

### *Elderly*

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

### 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 any component of this product
- patients with anuria
- patients who are hypersensitive to other sulphonamide derived medicines
- Arrow Losartan potassium and hydrochlorothiazide should not be administered with aliskiren in patients with diabetes (see section 4.5 **Interaction with other medicines and other forms of interaction**)

## **4.4 Special warnings and precautions for use**

### **Losartan-Hydrochlorothiazide**

#### *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 Arrow Losartan potassium and Hydrochlorothiazide as soon as possible (see section 4.6 **Fertility, pregnancy and lactation**).

#### *Hypersensitivity*

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**).

#### *Hepatic and Renal Impairment*

Arrow-Losartan potassium and Hydrochlorothiazide is not recommended for patients with hepatic impairment or severe renal impairment (creatinine clearance  $\leq$  30mL/min) (see section 4.2 **Dose and Method of Administration**).

### **Losartan**

#### *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; these changes may be reversible upon discontinuation of therapy.

## **Hydrochlorothiazide**

### ***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, hypomagnesaemia or hypokalaemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients.

### ***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**)

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.

### ***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**).

### ***Pregnancy***

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.

### ***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 ( $\geq 65$  years) and younger ( $<65$  years) patients.

### ***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 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 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-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 (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.

## **4.5 Interaction with other medicines and other forms of interaction**

### **Losartan**

In clinical pharmacokinetic trials, no medicine interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital (see Hydrochlorothiazide - Alcohol, barbiturates, or narcotics below), 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 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.

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 may be attenuated by NSAIDs including selective COX-2 inhibitors.

In some patients with compromised renal function (e.g., elderly 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 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.

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):* dosage adjustment of the antidiabetic medicine may be required.

*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.

*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***

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.

Although there is no experience with the use of a combination of losartan potassium 50 mg/hydrochlorothiazide 12.5 mg tablet 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 a combination of losartan potassium 50 mg/hydrochlorothiazide 12.5 mg tablet is administered during the second or third trimesters 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 Arrow Losartan potassium and Hydrochlorothiazide 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 Arrow-Losartan potassium and Hydrochlorothiazide, 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 Arrow-Losartan potassium and Hydrochlorothiazide for hypotension, oliguria, and hyperkalemia.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and foetus to unnecessary hazard including foetal or neonatal jaundice, thrombocytopenia and possibly other adverse reactions which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

### ***Lactation***

It is not known whether losartan is excreted in human milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the medicine, taking into account the importance of the medicine to the mother.

### ***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**

In clinical trials with losartan potassium - hydrochlorothiazide, no adverse experiences peculiar to this combination medicine have been observed. Adverse experiences have been limited to those that were reported previously with losartan potassium and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. The percentage of discontinuations of therapy was also comparable to placebo.

In general, treatment with losartan potassium - hydrochlorothiazide was well tolerated. For the most part, adverse experiences have been mild and transient in nature and have not required discontinuation of therapy.

In controlled clinical trials for essential hypertension, dizziness was the only adverse experience reported as medicine related that occurred with an incidence greater than placebo in one percent or more of patients treated with losartan potassium - hydrochlorothiazide.

In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy, losartan, often in combination with hydrochlorothiazide, was generally well tolerated. The most common medicine-related side effects were dizziness, asthenia/fatigue, and vertigo.

The following additional adverse reactions have been reported in post-marketing experience with losartan potassium - hydrochlorothiazide and/or in clinical trials or post-marketing use with the individual components:

*Neoplasms benign, malignant and unspecified (including cysts and polyps):* Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).

*Blood and the lymphatic system disorders:* Thrombocytopaenia anaemia, aplastic anaemia, haemolytic anaemia, leukopaenia, agranulocytosis.

*Immune system disorders:* Anaphylactic reactions, angioedema (including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue) has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other medicines including ACE inhibitors.

*Metabolism and nutrition disorders:* Anorexia, hyperglycaemia, hyperuricaemia, electrolyte imbalance including hyponatraemia and hypokalaemia.

*Psychiatric disorders:* Insomnia, restlessness

*Nervous system disorders:* Dysgeusia, headache, migraine, paraesthesias

*Eye disorders:* Xanthopsia, transient blurred vision.

*Cardiac disorders:* Palpitation, tachycardia.

*Vascular disorders:* Dose-related orthostatic effects, necrotising angiitis (vasculitis) (cutaneous vasculitis).

*Respiratory, thoracic and mediastinal disorders:* Cough nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, respiratory distress (including pneumonitis and pulmonary oedema).

*Gastrointestinal disorders:* Dyspepsia, abdominal pain, gastric irritation, cramping, diarrhoea, constipation, nausea, vomiting, pancreatitis, sialoadenitis.

*Hepato-biliary disorders:* Hepatitis, jaundice (intrahepatic cholestatic jaundice).

*Skin and subcutaneous tissue disorders:* Rash, pruritus, purpura (including Henoch-Schoenlein purpura), toxic epidermal necrolysis, urticaria, erythroderma, photosensitivity, cutaneous lupus erythematosus

*Musculoskeletal and connective tissue disorders:* Back pain, muscle cramps, muscle spasm, myalgia, arthralgia.

*Renal and urinary disorders:* Glycosuria, renal dysfunction, interstitial nephritis, renal failure.

*Reproductive system and breast disorders:* Erectile dysfunction/impotence.

*General disorders and administration site conditions:* Chest pain, oedema/swelling, malaise, fever, weakness.

*Investigations:* Liver function abnormalities.

### **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 and 5.1).

### **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://nzphvc.otago.ac.nz/reporting/>

## **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 hemodialysis.

## **Hydrochlorothiazide**

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

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

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: 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 hyperuricaemia.

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).

## **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 <sup>14</sup>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 <sup>14</sup>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/m<sup>2</sup>) (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 fetuses 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

24 April 2019

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
3.	Tablet description added.
4.4, 4.8, 5.1	Information regarding risk of non-melanoma skin cancer added.
4.5 & 4.6	Updated
4.8	Reporting of suspected adverse reactions advice added.
4.9	Contact details for National Poisons Centre added.
5.1	Pharmacotherapeutic group and ATC code added.