NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Spironolactone, 25 mg film-coated tablets
Spironolactone, 100 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Spironolactone 25 mg film-coated tablets contain 25 mg spironolactone.
Excipients with known effect: Lactose
Each tablet contains 75 mg lactose monohydrate.

Spironolactone 100 mg film-coated tablets contain 100 mg spironolactone.
Excipients with known effect: Lactose
Each tablet contains 300 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Spironolactone 25 mg film-coated tablets are white to pale white, round, biconvex tablets printed with “AD” on one side and no imprint on the other side.
25mg tablet diameter is approximately 8.1 mm.

Spironolactone 100 mg film-coated tablets are white to pale white, round, biconvex tablets printed with “AF” on one side and no imprint on the other side.
100mg tablet diameter is approximately 11.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension; oedematous conditions including congestive cardiac failure, cirrhosis of the liver, (with or without ascites) and the nephrotic syndrome; diagnosis and treatment of primary aldosteronism, as adjunctive therapy in malignant hypertension; in diuretic induced hypokalaemia/hypomagnesaemia when other measures are considered inappropriate or inadequate; prophylaxis of hypokalaemia in patients taking digitalis when other measures are considered inadequate or inappropriate, hirsutism.

Hirsutism in Females
Spironolactone is effective in the treatment of females with hirsutism, an androgen-related increase in facial and body hair. A reduction in hair growth, hair shaft diameter and hair pigmentation is seen.

Essential Hypertension
Spironolactone, when used alone, is effective in lowering both systolic and diastolic blood pressure. Spironolactone improves the hypotensive action of thiazide diuretics while at the same time reducing or preventing potassium loss due to the thiazide. Spironolactone enhances the effectiveness of other antihypertensive agents such as beta blockers, vasodilators, etc.

Congestive Cardiac Failure
Spironolactone, when used alone, is effective in the management of oedema and sodium retention associated with congestive cardiac failure. Spironolactone may be used in combination with a thiazide or other conventional diuretics for achieving diuresis in patients whose oedema is resistant to a thiazide or other

conventional diuretics. Unlike conventional diuretics spironolactone does not produce hypokalaemia. When administered with a thiazide or other conventional diuretics, spironolactone offsets hypokalaemia induced by these diuretics. The prevention of potassium loss is particularly important in the treatment of digitalised patients since digitalis intoxication may be precipitated if hypokalaemia is induced by conventional diuretic therapy.

Hepatic Cirrhosis with Ascites and Oedema
Spironolactone when used alone is frequently adequate for the relief of ascites and oedema associated with hepatic cirrhosis. Spironolactone provides a mild and even diuresis and prevents excessive potassium excretion caused by thiazide diuretics thus avoiding possible precipitation of hepatic coma.

Nephrotic Syndrome
Although glucocorticoids, whose anti-inflammatory activity appears to benefit the primary pathologic process in the renal glomerulus, should probably be employed first, spironolactone either alone or in combination with a conventional diuretic is useful for inducing diuresis.

Primary Hyperaldosteronism
Spironolactone may be used to establish the diagnosis of primary hyperaldosteronism by therapeutic trial. Spironolactone may also be used for the short-term pre-operative treatment of patients with primary hyperaldosteronism, long-term maintenance therapy for patients with discrete aldosterone-producing adrenal adenomas who are judged to be poor operative risks (or who decline surgery), and the long-term maintenance therapy for patients with bilateral micro or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism).

4.2 Dose and method of administration

Adults
Essential Hypertension: 50 mg/day to 100 mg/day which for difficult or severe cases may be gradually increased at 2-weekly intervals up to 200 mg/day. The daily dose may be given either in divided doses or as a single daily dose.

Treatment should be continued for at least 2 weeks to ensure an adequate response to therapy.

Dosage should subsequently be adjusted according to the response of the patient.

Oedematous Disorders: The daily dose may be given either in divided doses or as a single daily dose.

Congestive Cardiac Failure: Initial dose – 100 mg/day. In difficult or severe cases the dosage may be gradually increased up to 200 mg/day. When oedema is controlled, the usual maintenance level is 25 mg/day to 200 mg/day. Maintenance dose should be individually determined.

Cirrhosis: If urinary Na+/K+ ratio is greater than 1 (one) the recommended dose is 100 mg/day.
If the ratio is less than 1 (one) the recommended dose is 200 mg/day to 400 mg/day. Maintenance dosage should be individually determined.

Nephrotic Syndrome: Usually 100 mg/day to 200 mg/day. Spironolactone is not anti-inflammatory, has not been shown to affect the basic pathological process, and its use is only advised when treatment of the underlying disease, restriction of fluid intake and sodium intake, and the use of other diuretics do not provide an adequate response.

Children
Oedema in Children: The initial daily dosage is 3.3 mg/kg body weight daily in divided doses. Dosage should be adjusted on the basis of response and tolerance. The tablet may be ground or crushed and then suspended in water to make it easier to take.

Diagnosis and Treatment of Primary Aldosteronism
Spironolactone may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long Test: Spironolactone is administered at a daily dosage of 400 mg for 3 to 4 weeks.

Correction of hypokalaemia and hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short Test: Spironolactone is administered at a daily dosage of 400 mg for 4 days. If serum potassium increases during spironolactone administration but drops when spironolactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, spironolactone may be administered in doses of 100 mg to 400 mg daily in preparation for surgery. For patients who are considered unsuitable for surgery, spironolactone may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

Malignant Hypertension: Spironolactone should be used as adjunctive therapy only, where there is an excessive secretion of aldosterone, hypokalaemia and metabolic alkalosis. Initial dosage: 100 mg/day increased as necessary in two weekly intervals to 400 mg/day. Initial therapy should include a combination of other antihypertensive drugs and spironolactone. Do not automatically reduce the dose of other treatments as is recommended for essential hypertension.

Hypokalaemia/Hypomagnesaemia: Spironolactone administered at a dosage of 25 mg to 100 mg daily may be useful in treating diuretic-induced hypokalaemia and/or hypomagnesaemia when oral potassium and/or magnesium supplements are considered inappropriate.

Female Hirsutism: 100 mg/day to 200 mg/day in divided doses is usual however 50 mg/day has also been shown to be effective.

Clinical improvement is usually shown within 3 to 6 months and an initial course of treatment should continue for 12 months.

Spironolactone may be administered continuously or as a cyclical dosage for approximately 3 weeks out of every 4 weeks. Dosing from Day 5 to Day 21 of the menstrual cycle, with a drug free interval during menstruation has been effective.

Cyclical dosing may reduce menstrual irregularities in women with previously regular cycles.

Combined use with oestrogen-progestogen oral contraceptives may also be considered to provide both regular menstrual cycles and adequate contraception.

Method of administration
The tablets should be taken with meals.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Severe renal insufficiency (eGFR <30 mL per minute per 1.73 m^2), acute or progressive kidney disease (whether or not this is accompanied by anuria)
- Hyponatraemia
- Hyperkalaemia (serum potassium level > 5.0 mmol/L) at initiation
- Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements, or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB)

Spironolactone is contraindicated in paediatric patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Fluid and electrolyte balance
During long-term therapy with spironolactone, fluid and electrolyte status should be regularly monitored, especially in elderly patients. Administration of spironolactone is not recommended if plasma potassium levels are elevated and contra-indicated in severe renal insufficiency (See Section 4.3). During treatment with spironolactone, severe hyperkalaemia can occur, which may result in cardiac arrest (sometimes fatal) in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements.

Hyperkalaemia may be accompanied by paraesthesia, weakness, mild paralysis or muscle spasms and is difficult to distinguish clinically from hypokalaemia. ECG changes may be the first sign of disturbed potassium balance, although hyperkalaemia is not always accompanied by an abnormal ECG.

Combination with potent potassium-sparing diuretics such as triamterene and amiloride is contra- indicated in order to prevent hyperkalaemia and care should be taken to avoid administration of extra potassium

Impaired renal function
Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. The risk of hyperkalaemia increases with decreasing renal function. Therefore, these patients should be treated with caution.

Severe hepatic insufficiency
Caution is required in patients with hepatic disorders due to the risk of hepatic coma.

Carcinogenicity
Animal studies have shown that at high doses and after long-term use, spironolactone induces tumours. The significance of these data for clinical application is unclear. However, the benefits of therapy should be weighed against the possible long-term harm before initiating long-term use of spironolactone in young patients.

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

Paediatric population
Potassium-sparing diuretics should be used with caution in hypertensive paediatric patients with mild renal insufficiency because of the risk of hyperkalaemia. (Spironolactone is contraindicated for use in paediatric patients with moderate or severe renal impairment; see section 4.3).

Concomitant use of medicines known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia.

4.5 Interaction with other medicines and other forms of interaction

Interactions affecting spironolactone

Combinations causing hyperkalaemia
Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements, or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) is contraindicated because of the risk of hyperkalaemia (see Section 4.3).

The use of ACE inhibitors in combination with spironolactone may be accompanied by hyperkalaemia, especially in patients with impaired renal function. Concomitant use requires careful dosing and close monitoring of the electrolyte balance.

Spironolactone and ciclosporin coadministration not recommended, as both increase serum potassium level and possible serious life-threatening interactions.

Heparin, low molecular weight heparin:
Concomitant use of spironolactone with heparin or low molecular weight heparin may lead to severe hyperkalemia. Increased diuresis has been observed during concomitant use of spironolactone and heparin.

Non-Steroidal Anti-Inflammatory Drugs
Acetyl salicylic acid and indomethacin may attenuate the diuretic action of spironolactone due to inhibition of intrarenal synthesis of prostaglandins. Hyperkalemia has been associated with the use of indomethacin in combination with potassium-sparing diuretics.

Interactions affecting other medicinal products

Anti-coagulants
Spironolactone reduces the effect of anticoagulants.

Noradrenalin
Spironolactone reduces the vasoconstrictive effects of noradrenaline.

Anti-hypertensives
Spironolactone can potentiate the effect of antihypertensive agents. The dosage of such drugs, in particular ganglion-blocking drugs, can often be halved when spironolactone is added to the therapy.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Digoxin
Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity.

Alcohol, barbiturates or narcotics
Potentiation of orthostatic hypotension may occur.

Cholestyramine
Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spironolactone concurrently with cholestyramine.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia, may occur.

Other forms of interaction

Ammonium Chloride
Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spironolactone concurrently with ammonium chloride (e.g. in liquorice).

Plasma Cortisone levels
Spironolactone interferes with Mattingly's fluorimetric method for determination of plasma cortisone levels.

In addition to other medicinal products known to cause hyperkalaemia concomitant use of trimethoprim / sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

Prostate-specific antigen (PSA)
Spironolactone binds to the androgen receptor and may increase prostate-specific antigen (PSA) levels in abiraterone-treated prostate cancer patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are very limited data on the use of spironolactone during pregnancy in humans.

Experimental animal studies have shown reproductive toxicity associated with the anti-androgenic effect of spironolactone (see section 5.3). Spironolactone should not be used during pregnancy.

Diuretics can lead to reduced perfusion of the placenta and thus to impairment of intrauterine growth and are therefore not recommended for the standard therapy for hypertension and oedema during pregnancy.

Breastfeeding
Canrenone, the principal and active metabolite of spironolactone, appears in small quantities in human breast milk. Spironolactone should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from spironolactone-therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women.

Fertility
Spironolactone may induce impotence and menstrual irregularities (see section 4.8).

4.7 Effects on ability to drive and use machines

No data are available on the ability to drive. Undesirable effects such as dizziness, confusion and headache may occur. The possible occurrence of these undesirable effects should be taken into account when driving or using machines.

4.8. Undesirable effects

The undesirable effects are dependent on dose and duration of treatment.

The most common adverse effects are hyperkalaemia (9%), disorders of the reproductive system and breasts, including gynaecomastia, reported in 13% of patients (at a dose of less than 100 mg). Gynaecomastia appears to be related to both dosage level and duration of therapy and is usually reversible once treatment stops. Other very common undesirable effects include headache, digestive system disorders, diarrhoea, fatigue and drowsiness.

The undesirable effects below are classified in accordance with the following frequencies:
Very common (≥1/10), Common (≥1/100, < 1/10), Uncommon (≥1/1,000, <1/100), Rare (≥ 1/10,000, <1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Very rare: breast cancer

Blood and lymphatic system disorders
Rare: thrombocytopenia, eosinophilia, leukopenia (including agranulocytosis)

Immune system disorders
Rare: eczema (type 1 allergic reaction), hypersensitivity

Endocrine disorders
Not known: slight androgenic effects, including hirsutism.

Metabolism and nutrition disorders
Very common: hyperkalaemia in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements (see also section 4.4)

Common: hyponatraemia (in particular during combined intensive therapy with thiazide diuretics), hyperkalaemia in (1) patients with severe renal dysfunction, (2) patients receiving treatment with ACE inhibitors or potassium chloride, (3) the elderly, and (4) diabetic patients

Uncommon: acidity of the blood (acidosis) in patients with liver problems

Rare: insufficient fluid in the tissues (dehydration), porphyria, temporary increase in nitrogen levels in the blood and urine, hyperuricemia (may lead to gout in predisposed patients)

Not known: reversible hyperchloraemic metabolic acidosis – usually accompanied by hyperkalaemia has been reported in some patients with decompensated hepatic cirrhosis, even where renal function was normal.

Psychiatric disorders
Uncommon: confusion

Nervous system disorders
Very common: headache
Common: weakness, lethargy in patients with cirrhosis, tingling (paraesthesia)
Rare: paralysis, paraplegia of the limbs due to hyperkalaemia
Not known: dizziness, ataxia

Vascular disorders
Very rare: inflammation of the vessel walls (vasculitis)
Not known: mild hypotension

Gastrointestinal disorders
Very common: indigestion, diarrhoea
Common: nausea and vomiting
Very rare: gastric inflammation, gastric ulcers, intestinal haemorrhage, cramps

Hepatobiliary disorders
Very rare: hepatitis

Skin and subcutaneous tissue disorders
Uncommon: skin rash, urticaria, erythema, chloasma, pruritus, exanthema
Very rare: alopecia, eczema, erythema annulare centrifugum (EAC), hypertrichosis
Not known: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), Pemhigoid

Musculoskeletal and connective tissue disorders
Uncommon: muscle spasms, leg cramps

Very rare: systemic lupus erythematosus (SLE), Osteomalacia

Renal and urinary disorders
Uncommon: elevated serum creatinine levels

Very rare: acute renal failure

Reproductive system and breast disorders
Very common: Men: reduced libido, erectile dysfunction, impotence, enlargement of the mammary glands (gynaecomastia);

Women: breast disorders, tenderness of the breasts, menstrual disorders, deepening of the voice (in many cases irreversible)

Common: Women: changes in vaginal secretions, reduced libido, absence of periods (amenorrhoea), post-menopausal bleeding

General disorders and administration site conditions
Very common: fatigue, drowsiness
Common: malaise

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 via https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Overdose can manifest itself in the form of nausea and vomiting, and (more rarely) by drowsiness, confusion, skin rash or diarrhoea.

In addition, infertility can occur at very high doses (450 mg/day).

Hyponatraemia, or hyperkalaemia may be induced, but these effects are unlikely to be associated with acute overdosage. Symptoms of hyperkalaemia may manifest as paraesthesia, weakness, flaccid paralysis or muscle spasm and may be difficult to distinguish clinically from hypokalaemia. Electrocardiographic changes are the earliest specific signs of potassium disturbances. No specific antidote has been identified.

Improvement may be expected after withdrawal of the medicine.

If electrolyte balance disturbance and dehydration occur, treatment is symptomatic and supportive and may include replacement of fluids and electrolytes may be indicated. For hyperkalaemia, reduce potassium intake, administer potassium-excreting diuretics, intravenous glucose with regular insulin or oral ion-exchange resins.

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: cardiovascular system, diuretics, potassium-sparing diuretics, aldosterone antagonist.

ATC code: C03DA01
Spironolactone affects the kidney and the adrenal gland (as an antagonist of aldosterone in the renal tubuli and an inhibitor of aldosterone synthesis in high concentrations).

Spironolactone promotes diuresis in patients with oedema or ascites by increasing excretion of sodium in the urine. Potassium loss caused by thiazide diuretics is reduced. It has a gradual and prolonged action. The antihypertensive effect of spironolactone is based on water and salt depletion.

Severe heart failure: RALES
The RALES study was a multinational, double-blind study in 1663 patients with an ejection fraction of ≤ 35%, a history of New York Heart Association (NYHA) class IV heart failure within 6 months, and class III-IV heart failure at the time of randomisation. All patients were taking a loop diuretic, 97% were taking an ACE inhibitor and 78% were on digoxin (at the time this trial was conducted, beta-blockers were not widely used to treat heart failure and only 15% were treated with a beta- blocker). Patients with a baseline serum creatinine of >2.5 mg/dL or a recent increase of 25% or with a baseline serum potassium of >5.0 mEq/L were excluded. Patients were randomized 1:1 to spironolactone 25 mg orally once daily or matching placebo. Patients who tolerated 25 mg once daily had their dose increased to 50 mg once daily as clinically indicated. Patients who did not tolerate 25 mg once daily had their dosage reduced to 25 mg every other day. The primary endpoint for RALES was time to all-cause mortality. RALES was terminated early, after a mean follow-up of 24 months, because of a significant mortality benefit detected on a planned interim analysis. Spironolactone reduced the risk of death compared to placebo (mortality spironolactone 284/841 (35%); placebo 386/822 (46%); Risk reduction 30%; 95% confidence interval 18% to 40%; p<0.001). Spironolactone also significantly reduced the risk of cardiac death, primarily sudden death and death from progressive heart failure as well as the risk of hospitalisation for cardiac causes.

Paediatric population
There is a lack of substantive information from clinical studies on spironolactone in children. This is a result of several factors: the few trials that have been performed in the paediatric population, the use of spironolactone in combination with other agents, the small numbers of patients evaluated in each trial and the different indications studied. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in scientific literature.

5.2 Pharmacokinetic properties

Absorption
Approximately 70% of spironolactone is absorbed after oral administration. The bioavailability of spironolactone can be increased if it is taken with food. The clinical relevance of this effect is however not entirely clear. Following the administration of 100 mg of spironolactone daily for 15 days in non- fasted healthy volunteers, time to peak plasma concentration (tmax), peak plasma concentration (Cmax), and elimination half-life (t1/2) for spironolactone is 2.6 hr., 80ng/ml, and approximately 1.4hr., respectively. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites, tmax was 3.2 hr. and 4.3 hr., Cmax was 391 ng/ml and 181 ng/ml, and t1/2 was 13.8 hr. and 16.5 hr, respectively.

Distribution
Both spironolactone and canrenone are over 90% bound to plasma proteins.

*Biotransformatio*n
Spironolactone is extensively metabolised to active metabolites: including thiomethyl- spironolactone and canrenone.

Elimination
The plasma half-life of spironolactone is approximately 1.5 hours, that of 7 α-thiomethyl- spironolactone

approximately 9-12 hours and that of canrenone 10-35 hours. Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces. The renal action of a single dose of spironolactone reaches its peak after 7 hours, and activity persists for at least 24 hours.

Paediatric population
There are no pharmacokinetic data available in respect of use in paediatric population. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in the scientific literature.

5.3 Preclinical safety data

Spironolactone has been shown to be a tumorigen in chronic toxicity studies performed in rats with its proliferative effects manifested on endocrine organs, and the liver. In one study using 25, 75 and 250 times the usual daily human dose (2 mg/kg) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes.

In female rats, there was a statistically significant increase in malignant mammary tumours at the

mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg/kg), the range of effects included hepatocytomegaly, hyperplastic nodules, and hepato- cellular carcinoma; the last was not statistically significant at a value of p=0.05. Tumours were not observed in monkeys administered 20 mg/kg to 250 mg/kg daily for up to 52 weeks.

In a 2 year oral carcinogenicity study in which rats were administered 10 mg/kg/day, 30 mg/kg/day, 100 mg/kg/day, and 150 mg/kg/day of spironolactone, the range of proliferative effects observed was consistent with earlier studies. There were statistically significant increases at the higher doses in hepatocellular adenomas and testicular interstitial cell tumours in males, and in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant, but not dose-related, increase in benign uterine endometrial polyps in females. There was an increase in hepatocellular carcinomas in males at 150 mg/kg but this was not statistically significant. There was no significant increase in the incidence of mammary tumours.

The significance of these findings with respect to clinical use is not certain. However, it is likely that the effects in rats are secondary to the induction of hepatic P-450 metabolising enzymes in this species.

Spironolactone is metabolised to a minor extent to canrenone. Canrenone and canrenoic acid are the major metabolites of potassium canrenoate. A dose-related (above 20 mg/kg/day) incidence of myelocytic leukaemia was observed in rats fed daily doses of potassium canrenoate for a period of 1 year. In a long-term (2 year) oral carcinogenicity study of potassium canrenoate in rats, myelocytic leukaemia and hepatic, thyroid, testicular, and mammary tumours were observed. Potassium canrenoate did not produce a mutagenic effect in tests using bacteria or yeast. It did produce a positive mutagenic effect in several in vitro tests in mammalian cells following metabolic activation. In an in vivo mammalian system, potassium canrenoate was not mutagenic. An increased incidence of leukaemia was not observed in chronic rat toxicity or carcinogenicity studies conducted with spironolactone at doses up to 500 mg/kg/day.

Spironolactone was devoid of teratogenic effects in mice (0 mg/kg/day to 20 mg/kg/day). Rabbits receiving 20 mg/kg/day showed a reduced conception rate, increased resorption rate and a lower number of live births. No embryotoxic effects were seen in rats at doses up to 50 mg/kg/day but limited, dose-related teratogenic effects (hypoprolactinaemia and decreased ventral prostate and seminal vesicle weights in males; increased luteinizing hormone secretion and ovarian and uterine weights in females) were reported in one study at doses of approximately 50 mg/kg/day and 100 mg/kg/day. Feminisation of the external genitalia of male fetuses was reported in another study in rats at doses of approximately 200 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Pregelatinised corn starch
Calcium hydrogen phosphate anhydrous
Povidone K25
Peppermint oil
Purified talc
Silica, colloidal anhydrous
Magnesium stearate

Film coating:
Hypromellose
Macrogol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 3 years

Bottles: 2 years,
In-use shelf-life after first opening: 3 months.

6.4 Special precautions for storage

Store at or below 25°.
Store in the original pack in order to protect from light.

6.5 Nature and contents of container

Film coated tablets are packed in PVC-Aluminium blister packs and HDPE bottles.

Pack sizes:

Blister pack: 100 tablets

HDPE bottle: 250 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Max Health Ltd
PO Box 44452
Pt Chevalier
Auckland 1246
Telephone: (09) 815 2664.

9. DATE OF FIRST APPROVAL

22 July 2021

10. DATE OF REVISION OF THE TEXT

21 March 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.5	Addition of prostate specific antigen (PSA) increase in use of spironolactone during abiraterone treatment in prostate cancer patients.
4.8	Update CARM URL address
4.9	Addition of Overdose text 'For risk assessment'
8.0	Update sponsor address