NEW ZEALAND DATA SHEET

SPIRACTIN

1. Product Name

SPIRACTIN, 25 mg, 100 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 25 mg or 100 mg of spironolactone.

SPIRACTIN contains sugars as lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

25 mg Tablets: 7 mm normal convex pale orange tablet marked α on one side and $\frac{SP}{1}$ on the other.

100 mg Tablets: 11 mm normal convex pale orange tablet marked α on one side and $\frac{SP}{2}$ on the other.

4. Clinical Particulars

4.1 Therapeutic indications

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

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.

Use of spironolactone should be considered only after all other alternatives of non-drug therapy has been explored. For women of child-bearing age, see section 4.3 and 4.6.

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.

Idiopathic oedema

Aldosterone may play an important role in the aetiology of idiopathic oedema and in many instances spironolactone therapy has achieved favourable results.

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 preoperative treatment of patients with primary hyperaldosteronism, long term maintenance therapy for patients with discrete 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 two weekly intervals up to 200 mg per 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 since an adequate response may not occur before this time. Dosage should subsequently be adjusted according to the response of the patient.

Spironolactone may potentiate the action of diuretics or other antihypertensive drugs and their dose should first be reduced by at least 50% when spironolactone is added to the regimen, and then adjusted as necessary.

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.

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 and sodium intake, and the use of other diuretics do not provide adequate response.

Idiopathic oedema

Usual dosage 100 mg/day

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 may include a combination of other antihypertensive drugs and spironolactone. Do not automatically reduce the dose of other treatments as is recommended for essential hypertension.

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 (see section 4.6).

Special populations

Children and adolescents

Oedema
The initial daily dosage should provide approximately 3.3 mg/kg. For small children, spironolactone

tablets may be pulverized and administered as a suspension in cherry syrup. When refrigerated, such a suspension is stable for 1 month.

4.3 Contraindications

- acute renal insufficiency
- significant impairment of renal function
- anuria
- Addison's disease or other conditions associated with hyperkalaemia (see section 4.4.),
- hyperkalaemia
- pregnancy
- hypersensitivity to spironolactone (or to any excipients listed in section 6.1)
- with concomitant use of eplerenone.

4.4 Special warnings and precautions for use

Concomitant use of spironolactone with angiotensin converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin, other drugs or conditions known to cause hyperkalaemia, potassium supplements, a diet rich in potassium, including salt substitutes containing potassium, or other potassium sparing agents is not recommended as it may lead to severe hyperkalaemia.

Hyperkalaemia may be fatal in patients with severe heart failure (New York Heart Association [NYHA] class III-IV). Potassium and creatinine levels should be closely monitored 1 week after initiation or monthly for the first 3 months, then quarterly for a year, and then every 6 months when increasing the dose of spironolactone. Concomitant use of spironolactone and other potassium-sparing diuretics in patients with severe heart failure should be avoided. If serum potassium is > 3.5 mEq/L, oral potassium supplements should be avoided. Treatment with spironolactone should be discontinued or interrupted in patients with serum potassium > 5 mEq/L or with serum creatinine > 4 mg/dL.

Periodic estimation of serum electrolytes is desirable due to the possibility of hyperkalaemia, hyponatraemia and possible transient blood urea nitrogen (BUN) elevation especially in the elderly and/or patients with pre-existing impaired renal or hepatic function, in whom the risk/benefit ratio should always be weighed.

Reversible hyperchloraemic metabolic acidosis, usually in association with hyperkalaemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function.

The safety of spironolactone for the treatment of hirsutism in women of child-bearing age has not been established by specific long-term clinical trials. Epidemiological studies are also inadequate to establish the safety of long-term use in this population.

Use in hepatic impairment

See section 4.4.

Use in renal impairment

See section 4.3.

Use in the elderly

See section 4.4.

Paediatric use

No data available.

Effect on laboratory tests

Spironolactone can interfere with assays for plasma digoxin concentrations.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of drugs known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia (see section 4.4).

The administration of potassium supplements, a diet rich in potassium, including salt substitutes, or of other potassium sparing agents is not recommended as it may induce hyperkalaemia.

Hyperkalaemia has been associated with the use of indomethacin or ACE inhibitors in combination with potassium sparing diuretics.

Spironolactone reduces the vascular responsiveness to noradrenaline. Therefore, caution should be exercised in the management of patient subjected to regional or general anaesthesia while they are being treated with spironolactone.

As carbenoxolone may cause sodium retention and thus decrease the effectiveness of spironolactone, concurrent use of the two agents should be avoided.

Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. It may be necessary to reduce the digoxin dose when spironolactone is administered, and the patient should be carefully monitored to avoid over-or under-digitalisation.

Spironolactone may have an additive effect when given concomitantly with other diuretics and antihypertensive agents. The dose of such medicines may need to be reduced when spironolactone is added to the treatment regimen.

Non-steroidal anti-inflammatory drugs such as aspirin, indomethacin, and mefenamic acid may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins and have been shown to attenuate the diuretic effect of spironolactone.

Spironolactone enhances the metabolism of antipyrine.

Hyperkalaemic metabolic acidosis has been reported in patients given spironolactone concurrently with ammonium chloride or cholestyramine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B3.

Experimentally, passive transfer of potassium sparing diuretics across the human placenta has been demonstrated. Maternal treatment during pregnancy may result in electrolyte disturbances in the foetus. Spironolactone should not be used in pregnancy (see section 4.3). Women of child-bearing potential should employ adequate contraception (i.e. oral contraceptives or IUDs) during administration of spironolactone, and the drug should be stopped if pregnancy occurs or is suspected.

Use during lactation

Canrenone, an active metabolite of spironolactone, appears in breast milk. If use of the drug is deemed essential an alternative method of infant feeding should be instituted.

Fertility

For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Somnolence and dizziness have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

4.8 Undesirable effects

Gynaecomastia may develop in association with the use of spironolactone, and physicians should be alert to its possible onset. The development of gynaecomastia appears to be related to both dosage level duration of therapy and is normally reversible when spironolactone is discontinued. In rare instances some breast enlargement may persist.

Other adverse reactions that have been reported in association with spironolactone are: gastrointestinal symptoms including cramping, diarrhoea, nausea, vomiting, gastric bleeding, ulceration and gastritis; drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, impotence, irregular menses or amenorrhoea, post-menopausal bleeding, malaise, benign breast neoplasm, breast pain, leucopenia (including agranulocytosis), thrombocytopenia, abnormal hepatic function, electrolyte disturbances, hyperkalaemia, leg cramps, dizziness, changes in libido, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, hypertrichosis, pruritus, rash and acute renal failure.

Carcinoma of breast has been reported in patients taking spironolactone, but a cause and effect relationship has not been established.

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

Symptoms

Overdosage may be manifested by nausea and vomiting, dizziness and (more rarely) by drowsiness, mental confusion, maculopapular or erythematous rash or diarrhoea. Electrolyte imbalances and dehydration may occur. Hyperkalaemia may be produced; symptoms include paraesthesia, weakness, flaccid paralysis and tetany.

The earliest signs are characteristic electrocardiographic abnormalities including tall “tent shaped” T waves, decreased amplitude of the P waves and widening of the QRS complex. Delayed onset of hyperkalaemia has been reported after acute ingestion of spironolactone (peak levels at 24 hours and 32 hours).

Treatment

Symptomatic and supportive measure should be employed. There is no specific antidote. Support respiratory and cardiac functions. Treat fluid depletion, electrolyte imbalances, and hypotension by established procedures.

Severity of intoxication should be based on clinical findings and serial determination of serum potassium levels. Monitoring plasma levels of spironolactone is not clinically useful.

Hyperkalaemia can be treated promptly by the rapid intravenous administration of glucose (20% to 50%) and regular insulin, using 0.25 to 0.5 units of insulin per gram of glucose. Potassium excreting diuretics and ion exchange resins may also be administered, repeating as required.

Spironolactone should be discontinued and potassium intake (including dietary potassium) restricted.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aldosterone antagonists, ATC code: C03DA01

Mechanism of action

Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone dependent sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium is retained. Spironolactone acts both as a diuretic and as an antihypertensive agent. It may be given alone or with other diuretic agents that act more proximally in the renal tubule.

Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism, Oedematous states in which secondary aldosteronism is usually involved include congestive cardiac failure, hepatic cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for oedema and ascites in those conditions.

Spironolactone is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension.

Through its action in antagonising the effect of aldosterone, spironolactone inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss.

Spironolactone has not been demonstrated to elevate serum uric acid, to precipitate gout or to alter carbohydrate metabolism.

Spironolactone has moderate anti-androgenic activity in humans by inhibition of the interaction between dihydrotestosterone and the intracellular androgen receptor. It also inhibits several steps in ovarian steroidogenesis resulting in lowered plasma levels of testosterone and some other weak androgenic steroids. Through this activity spironolactone is effective in the treatment of female hirsutism.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

In the human, the bioavailability of spironolactone from orally administered spironolactone tablets exceeds 90% when compared with an optimally-absorbed solution (spironolactone in polyethylene glycol 400).

Food may increase the bioavailability of spironolactone – the clinical relevance of this effect is uncertain.

Metabolism

Spironolactone is rapidly and extensively metabolised. Approximately 25% to 30% of the dose administered is converted to canrenone. The sulphur-containing products are the predominant metabolites and together with spironolactone are thought to be primarily responsible for the

therapeutic effects of the medicine. Canrenone attains peak serum levels at two to four hours following single oral administration. Canrenone plasma concentrations decline in two distinct phases, being rapid in the first 12 hours and slower from 12 to 96 hours. The log-linear phase half-life of canrenone, following multiple doses of spironolactone, is between 13 and 24 hours. Both spironolactone and canrenone are more than 90% bound to plasma proteins.

Excretion

The metabolites of spironolactone are excreted primarily in urine, but also in bile.

5.3 Preclinical safety data

Effects on Fertility

In animal studies, spironolactone was devoid of teratogenic effects in mice and rabbits at oral doses up to 20 mg/kg/day, and in rats at dietary doses up to 50 mg/kg/day. However, increased resorption rate was seen at 20 mg/kg/day in rabbits, and the incidence of stillbirths was increased in rats dosed at 50 mg/kg/day. Subcutaneous administration of spironolactone (approximately 50 mg/kg/day to 100 mg/kg/day) to rats during late pregnancy caused endocrine dysfunction in both sexes of offspring 70-80 days after birth (hypoprolactinaemia and decreased ventral prostate and seminal vesicle weights in males; increased luteinizing hormone secretion and ovarian and uterine weights in females). Feminisation of the external genitalia of male foetuses was reported in another study in rats at oral doses of approximately 200 mg/kg/day. Subcutaneous administration of spironolactone to neonatal female mice caused histological changes in the cervicovaginal epithelium that were similar to those caused by diethylstilboestrol (a drug which causes vaginal neoplasia in adulthood following *in utero* exposure).

The risk of demasculinisation of the male foetus will only occur from about 6 weeks post conception onwards, hence if inadvertent spironolactone administration is stopped at an early stage the risk to the male foetus is small.

Genotoxicity

Spironolactone was not mutagenic in the Ames test using five strains of *Salmonella typhimurium* with or without metabolic activation.

Carcinogenicity

Spironolactone has been shown to be tumourigenic in chronic toxicity studies performed in rats. It should be used only for approved indications. Unnecessary use of this drug should be avoided.

In chronic toxicity studies of spironolactone in rats, changes were observed in the endocrine organs, and the liver. In one study using dietary doses of 50 mg/kg/day, 150 mg/kg/day and 500 mg/kg/day there was a statistically significant dose-related increase in benign adenomas of thyroid follicular cells and testicular interstitial cells. 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, which included hyperplastic nodules and hepatocellular carcinomas at the mid-and high doses.

In a two 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 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 known.

A dose related (above 30 mg/kg/day) incidence of myelocytic leukaemia was observed in rats fed daily doses of potassium canrenoate for a period of 1 year. Canrenone and canrenoic acid are the major metabolites of potassium canrenoate. Spironolactone is also metabolised to canrenone. In long term (2 year) oral carcinogenicity studies 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. The recommended human dose of spironolactone is 1.4 mg/kg/day to 5.7 mg/kg/day.

6. Pharmaceutical Particulars

6.1 List of excipients

Each SPIRACTIN tablet also contains:

- quinoline yellow
- sunset yellow
- erythrosine
- polysorbate
- peppermint oil
- povidone
- microcrystalline cellulose
- starch
- sodium starch glycollate
- talc
- magnesium stearate
- lactose.

Sulphites and galactose may be present in this product in trace amounts.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

HDPE bottle with PP-CRC. Pack size of 100 tablets.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

20 March 1980

10. Date of Revision of the Text

13 October 2021

Section	Summary of Changes
2	Statement updated to state “contains sugars as lactose” from “contains lactose”.