SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

ALDACTONE® 25 tablets

ALDACTONE® 100 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALDACTONE 25: Each tablet contains 25 mg spironolactone.

ALDACTONE 100: Each tablet contains 100 mg spironolactone.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

ALDACTONE 25: 8,8 mm diameter, white, round, biconvex, film-coated tablets stamped SEARLE 39 on one side and plain on the other with a characteristic peppermint odour.

ALDACTONE 100: 11,1 mm diameter, white, round, biconvex, film-coated tablets stamped SEARLE 134 on one side and plain on the other with a characteristic peppermint odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Short-term preoperative treatment of patients with primary hyperaldosteronism

- Congestive heart failure (alone or in combination with standard therapy), including severe heart failure (NYHA class III-IV)
- Conditions in which secondary hyperaldosteronism may be present, including liver cirrhosis accompanied by oedema and/or ascites, nephrotic syndrome, and other oedematous conditions (alone or in combination with standard therapy)
- Diuretic-induced hypokalaemia/hypomagnesaemia as adjunctive therapy
- Establishing a diagnosis of primary hyperaldosteronism

4.2 Posology and method of administration

Posology

For adults, the daily dose may be given in divided doses or as a single daily dose.

Essential hypertension

The usual adult dose is 50 mg to 100 mg per day, which for difficult or severe cases may be gradually increased at intervals of 2 weeks up to 200 mg per day. Treatment should be continued for at least 2 weeks to ensure an adequate response to therapy. Dose should be adjusted as necessary.

Congestive heart failure

An initial daily dose of 100 mg of ALDACTONE administered in either single or divided doses is recommended but may range from 25 mg to 200 mg daily. Maintenance dose should be individually determined.

Severe heart failure in conjunction with standard therapy (NYHA Class III-IV)

Treatment in conjunction with standard therapy should be initiated at a dose of ALDACTONE 25 mg once daily in patients with a serum potassium ≤ 5,0 mmol/L and serum creatinine ≤ 220 µmol/L. Patients who tolerate 25 mg once daily may have their dose increased to 50 mg once daily as clinically indicated. Patients who do not tolerate 25 mg once daily may have their dose reduced to 25 mg every other day. See section

4.4, *Hyperkalaemia in patients with severe heart failure*, for advice on monitoring serum potassium and serum creatinine.

Cirrhosis

If urinary Na+/K+ ratio is greater than 1,0, the usual adult dose is 100 mg per day. If the ratio is less than 1,0, the usual adult dose is 200 mg to 400 mg per day. Maintenance dose should be individually determined.

Nephrotic syndrome

The usual adult dose is 100 mg to 200 mg per day. ALDACTONE has not been shown to affect the basic pathological process, and its use is advised only if other therapy is ineffective.

Hypokalaemia/hypomagnesaemia

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.

Diagnosis and treatment of primary hyperaldosteronism

ALDACTONE may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long test: Daily adult dose of 400 mg for 3 to 4 weeks. Correction of hypokalaemia and of hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short test: Daily adult dose of 400 mg for 4 days. If serum potassium increases during ALDACTONE administration, but drops when ALDACTONE is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

Short-term preoperative treatment of primary hyperaldosteronism

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

Paediatric population

Initial daily dosage is 3 mg/kg body weight given in divided doses. Dosage should be adjusted on the basis of response and tolerance. ALDACTONE is insoluble in water but the tablets may be crushed and given in suspension if necessary.

Method of administration

For oral use.

4.3 Contraindications

ALDACTONE is contraindicated in adult and paediatric patients with:

- hypersensitivity to spironolactone or to any of the excipients of ALDACTONE (listed in section 6.1)
- acute renal insufficiency
- rapidly progressing impairment of renal function
- anuria
- hyperkalaemia
- concomitant use of eplerenone
- Addison’s disease

4.4 Special warnings and precautions for use

Concomitant use of spironolactone, such as contained in ALDACTONE, with other potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or other medicines

or conditions known to cause hyperkalaemia, potassium supplements, a diet rich in potassium, or salt substitutes containing potassium, may lead to severe hyperkalaemia.

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.

Caution should be observed in the presence of liver disease as hepatic coma may be precipitated in susceptible subjects. Periodic estimation of serum electrolytes may be desirable.

Hyperkalaemia in patients with severe heart failure

Hyperkalaemia may be fatal. It is critical to monitor and manage serum potassium in patients with severe heart failure receiving ALDACTONE. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium > 3,5 mmol/L. The recommended monitoring for potassium and creatinine is one week after initiation or increase in dose of ALDACTONE, monthly for the first 3 months, then quarterly for a year, and then every 6 months. Discontinue or interrupt treatment for serum potassium > 5 mmol/L or for serum creatinine > 350 µmol/L (see section 4.2, *Severe heart failure in conjunction with standard therapy (NYHA Class III-IV)*.

4.5 Interaction with other medicines and other forms of interaction

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

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

ALDACTONE reduces vascular responsiveness to norepinephrine (noradrenaline). Caution should be exercised in the management of patients subjected to anaesthesia while they are being treated with ALDACTONE.

ALDACTONE has been shown to increase the half-life of digoxin.

Aspirin, and other NSAIDS such as 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 ALDACTONE.

ALDACTONE enhances the metabolism of antipyrine.

ALDACTONE can interfere with assays for plasma digoxin concentrations.

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

Coadministration of ALDACTONE with carbenoxolone may result in decreased efficacy of either medicine.

ALDACTONE binds to the androgen receptor and may increase prostate specific antigen (PSA) levels in abiraterone-treated prostate cancer patients. Use with abiraterone is not recommended.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

Feminisation has been observed in male rat foetuses.

Breastfeeding

Metabolites of spironolactone have been detected in breast milk. If use of ALDACTONE is considered essential, an alternative method of infant feeding should be instituted.

4.7 Effects on ability to drive and use machines

Somnolence and dizziness have been reported to occur. Caution is advised when driving or operating machinery until the response to treatment with ALDACTONE has been determined.

4.8 Undesirable effects

The following side effects have been reported in association with ALDACTONE therapy.

Tabulated summary of adverse reactions

The table below lists the adverse reactions by system organ class and frequency using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Side effects**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	Benign breast neoplasm (male)
Blood and lymphatic system disorders	Frequency not known (cannot be estimated from available data)	Agranulocytosis, leukopenia, thrombocytopenia

Metabolism and nutrition disorders	Very common	Hyperkalaemia
	Uncommon	Electrolyte imbalance
Psychiatric disorders	Common	Confusional state
	Frequency not known (cannot be estimated from available data)	Libido disorder
Nervous system disorders	Common	Dizziness
Gastrointestinal disorders	Common	Nausea
	Frequency not known (cannot be estimated from available data)	Gastrointestinal disorder
Hepato-biliary disorders	Uncommon	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Uncommon	Urticaria
	Frequency not known (cannot be estimated from available data)	Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Drug reaction with eosinophilia and systemic symptoms (DRESS), alopecia, hypertrichosis

Musculoskeletal, connective tissue and bone disorders	Common	Muscle spasms
Renal and urinary disorders	Common	Acute kidney injury
Reproductive system and breast disorders	Common	Gynaecomastia*, breast pain (male)
	Uncommon	Menstrual disorder, breast pain (female)
General disorders and administration site conditions	Common	Malaise
* Gynaecomastia may be reversible when ALDACTONE is discontinued.		

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Acute overdosage may be manifested by drowsiness, mental confusion, nausea, vomiting, dizziness or diarrhoea.

Hyperkalaemia

Electrocardiographic changes give the earliest indications of pathologically disturbed serum potassium levels. In the event of hyperkalaemia, discontinue ALDACTONE, reduce potassium intake and administer potassium-excreting diuretics and intravenous glucose with insulin or an oral ion-exchange resin as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 18.1 Diuretics.

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.

5.2 Pharmacokinetic properties

Spironolactone is metabolised to sulfur-containing medicines that are thought to be primarily responsible, together with spironolactone, for the therapeutic effects of the medicine. The following pharmacokinetic data were obtained from 12 healthy volunteers following the administration of 100 mg of spironolactone daily for 15 days. On the 15th day, spironolactone was given immediately after a low-fat breakfast and blood was drawn thereafter.

	Accumulation factor: AUC (0 - 24 hours, day 15)/ AUC (0 - 24 hours, day 1)	Mean peak serum concentration	Mean (SD) elimination half-life

7-α - (thiomethyl) spirolactone (TMS)	1,25	391 ng/mL at 3,2 hours	13,8 hours (6,4)
6-ß-hydroxy-7- α (thiomethyl) spirolactone (HTMS)	1,50	125 ng/mL at 5,1 hours	15,0 hours (4,0)
Canrenone (C)	1,41	181 ng/mL at 4,3 hours	16,5 hours (6,3)
Spironolactone	1,30	80 ng/mL at 2,6 hours	Approximately 1,4 hours (0,5) (ß half-life)

The pharmacological activity of spironolactone metabolites in man is not known. However, in the adrenalectomised rat, the antimineralocorticoid activities of the metabolites C, TMS, and HTMS, relative to spironolactone, were 1,10; 1,28; and 0,32 respectively. Relative to spironolactone, their binding affinities to the aldosterone receptors in rat kidney slices were 0,19; 0,86; and 0,06 respectively.

In humans the potencies of TMS and 7- α-thiospirolactone in reversing the effects of the synthetic mineralocorticoid, fludrocortisone, on urinary electrolyte composition were 0,33 and 0,26 respectively, relative to spironolactone. However, since the serum concentrations of these steroids were not determined, their incomplete absorption and/or first-pass metabolism could not be ruled out as a reason for their reduced *in vivo* activities.

Spironolactone and its metabolites are more than 90 % bound to plasma proteins. The metabolites are excreted primarily in the urine and secondarily in bile.

The effect of food on spironolactone absorption was assessed in a single-dose study of 9 healthy volunteers. Food increased the bioavailability of unmetabolised spironolactone by almost 100 %. The clinical importance of this finding is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium sulfate dihydrate

Hydroxypropyl methylcellulose

Magnesium stearate

Maize starch

Opaspray® white

Peppermint flavour

Polyethylene glycol

Povidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store in a dry place at or below 25 °C.

6.5 Nature and contents of container

ALDACTONE 25: Blisters containing 60 or 100 tablets.

ALDACTONE 100: Blisters of 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION/REFERENCE NUMBERS

ALDACTONE 25 mg: H1941 (Act 101/1965)

ALDACTONE 100 mg: H/18.1/2

9. DATE OF FIRST AUTHORISATION

ALDACTONE 25: Not applicable (Old medicine)

ALDACTONE 100: 07 May 1975

10. DATE OF REVISION OF THE TEXT

03 June 2022

BOTSWANA: S2

ALDACTONE 100 mg

Reg. No.: B9311370

NAMIBIA: S2 ALDACTONE 100 mg Reg. No.: 90/18.1/001291
ZIMBABWE: PP ALDACTONE 25 mg Reg. No.: 84/12.5.1/1839