SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

ALDACTONE® 25 tablets

ALDACTONE® 100 tablets

COMPOSITION:

ALDACTONE 25: Each tablet contains 25 mg spironolactone

ALDACTONE 100: Each tablet contains 100 mg spironolactone.

ALDACTONE tablets contain the following inactive ingredients:

Calcium sulfate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, maize starch, Opaspray® white, peppermint flavour, polyethylene glycol and povidone.

PHARMACOLOGICAL CLASSIFICATION:

A 18.1 Diuretics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

Pharmacokinetic properties:

Spironolactone is metabolised to sulphur-containing products 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 hr, day 15)/AUC (0-24 hr, day 1)	**Mean Peak Serum Concentration**	**Mean (SD) Elimination Half-Life**
7-α - (thiomethyl) spirolactone (TMS)	1,25	391 ng/ml at 3,2 hr	13,8 hr (6,4)
6-ß-hydroxy-7- α (thiomethyl) spirolactone (HTMS)	1,50	125 ng/ml at 5.1 hr	15,0 hr (4,0)
Canrenone (C)	1,41	181 ng/ml at 4,3 hr	16,5 hr (6,3)
Spironolactone	1,30	80 ng/ml at 2,6 hr	Approximately 1,4 hr (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.

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

CONTRAINDICATIONS:

ALDACTONE is contraindicated in patients with:

- hypersensitivity to spironolactone or to any of the inert ingredients

- acute renal insufficiency
- rapidly progressing impairment of renal function
- anuria
- hyperkalaemia
- concomitant use of eplerenone
- Addison's disease

WARNINGS AND SPECIAL PRECAUTIONS:

Concomitant use of spironolactone, such as contained in ALDACTONE, with other potassium-sparing diuretics, ACE inhibitors, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or potassium supplements, a diet rich in potassium, or salt substitutes containing potassium, may lead to severe hyperkalaemia.

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.

Hyperkalemia 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 DOSAGE AND DIRECTIONS FOR USE: For severe heart failure.

Effects on ability to drive and operate machinery:

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.

INTERACTIONS:

ALDACTONE may have an additive effect when given concomitantly with other diuretics, antihypertensive agents. 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 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.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

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 to 100 mg per day, which for difficult or severe cases may be gradually increased at intervals of two weeks up to 200 mg/day. Treatment should be continued for at least two 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 to 200 mg daily. Maintenance dose should be individually determined.

For 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 WARNINGS AND SPECIAL PRECAUTIONS, 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/day. If the ratio is less than 1,0, the usual adult dose is 200 to 400 mg/day. Maintenance dose should be individually determined.

Nephrotic syndrome:

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

Children:

Initial dosage is 3 mg/kg body weight daily 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.

Hypokalaemia/Hypomagnesaemia:

25 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 or the diagnosis of primary hyperaldosteronism.

Short test: Daily adult dose of 400 mg for four 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 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.

SIDE EFFECTS:

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

System Organ Class	Frequency	Side Effects
Neoplasms benign and malignant (incl cysts and polyps)	Less frequent	Benign breast neoplasm
Blood and the lymphatic system disorders	Less frequent	Leucopenia (including agranulocytosis), thrombocytopenia
Metabolism and nutrition disorders	Less frequent	Electrolyte disturbances, hyperkalaemia
Psychiatric disorders	Less frequent	Confusion, changes in libido
Nervous system disorders	Less frequent	Dizziness
Gastrointestinal disorders	Frequent	Gastrointestinal disturbances, nausea
Hepato-biliary disorders	Less frequent	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash, urticaria, alopecia, hypertrichosis
Musculoskeletal, connective tissue and bone disorders	Less frequent	Leg cramps
Renal and urinary disorders	Less frequent	Acute renal failure
Reproductive system and breast disorders	Frequent	Gynaecomastia*, menstrual disorders
	Less frequent	Breast pain
General disorders and administration site conditions	Frequent	Malaise

* Gynaecomastia may be reversible when ALDACTONE is discontinued.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

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.

PRESENTATION:

ALDACTONE 25: Blisters containing 60 or 100 tablets.

ALDACTONE 100: Blisters of 30 tablets.

STORAGE INSTRUCTIONS:

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

Keep out of reach of children.

REGISTRATION/REFERENCE NUMBERS:

ALDACTONE 25 mg: H1941 (Act 101/1965)

ALDACTONE 100 mg: H/18.1/2

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

19 February 2016

NAMIBIA: S2 ALDACTONE 100 mg Reg. No.: 90/18.1/001291	BOTSWANA: S2 ALDACTONE 100 mg Reg. No.: B9311370	ZIMBABWE: PP ALDACTONE 25 mg Reg. No.: 84/12.5.1/1839