

# DATA SHEET

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## NAME OF MEDICINE

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ALDACTONE

Spironolactone 25 mg & 100 mg tablets

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## PRESENTATION

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### **ALDACTONE 25 mg**

Tablet (11/32 inch diameter), round, biconvex, buff coloured, peppermint flavoured, film coated, stamped 'SEARLE' over 39 on one side and unmarked on the other, each containing spironolactone B.P. 25 mg.

### **ALDACTONE 100 mg**

Tablet (7/16 inch diameter), round, biconvex, buff coloured, peppermint flavoured, film coated, stamped 'SEARLE' over 134 on one side and unmarked on the other, each containing spironolactone B.P. 100 mg.

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## USES

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### **Actions**

ALDACTONE (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. ALDACTONE acts as a potassium-sparing diuretic by causing increased amounts of sodium and water to be excreted, while potassium and magnesium are conserved.

ALDACTONE acts both as a diuretic and as an antihypertensive agent. It may be given alone or with other diuretic agents which 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 the nephrotic syndrome. By competing with aldosterone for receptor sites, ALDACTONE provides effective therapy for the oedema and ascites in those conditions.

ALDACTONE 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, ALDACTONE inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss.

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

ALDACTONE 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 ALDACTONE is effective in the treatment of female hirsutism.

## Pharmacokinetics

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

Spironolactone is rapidly and extensively metabolised. Approximately 25% to 30% of the dose administered is converted to canrenone. Canrenone and 7- $\alpha$ -(thiomethyl) spironolactone are its active metabolites. The activity of canrenone is reported to be 10 - 33% that of spironolactone. Both spironolactone and canrenone are more than 90-percent bound to plasma proteins. Food increases the bioavailability of spironolactone by increasing the absorption and possibly decreasing the first-pass metabolism of spironolactone.

ALDACTONE has a gradual onset of diuretic action with a maximum effect being reached on the third day of therapy. Diuresis continues for two or three days after discontinuation.

Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration ( $t_{max}$ ), peak plasma concentration ( $C_{max}$ ), and elimination half-life ( $t_{1/2}$ ) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 hr., respectively. For the 7- $\alpha$ -(thiomethyl) spironolactone and canrenone metabolites  $t_{max}$  was 3.2 hr. and 4.3 hr.,  $C_{max}$  was 391 ng/ml and 181 ng/ml, and  $t_{1/2}$  was 13.8 hr. and 16.5 hr., respectively.

Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

## 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

ALDACTONE 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

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

### Congestive Cardiac Failure

ALDACTONE, when used alone, is effective in the management of oedema and sodium retention associated with congestive cardiac failure. ALDACTONE 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 ALDACTONE does not produce hypokalaemia. When administered with a thiazide or other conventional diuretics ALDACTONE 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

ALDACTONE when used alone is frequently adequate for the relief of ascites and oedema associated with hepatic cirrhosis. ALDACTONE 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, ALDACTONE either alone or in combination with a conventional diuretic is useful for inducing diuresis.

### Primary Hyperaldosteronism

ALDACTONE may be used to establish the diagnosis of primary hyperaldosteronism by therapeutic trial. ALDACTONE may also be used for the short-term preoperative 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).

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## DOSAGE AND ADMINISTRATION

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### Adults

Essential Hypertension: 50 to 100 mg per day which for difficult or severe cases may be gradually increased at two 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 two 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 – 200 mg/day. Maintenance dose should be individually determined.

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

Nephrotic Syndrome: Usually 100-200 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.

### 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. For small children, ALDACTONE tablets may be pulverised and administered as a suspension with a few drops of glycerine and adding cherry syrup. When refrigerated, such a suspension is stable for one month.

### Diagnosis and Treatment of Primary Aldosteronism

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

Long Test: ALDACTONE is administered at a daily dosage of 400 mg for three to four weeks. Correction of hypokalaemia and of hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short Test: ALDACTONE is administered at a daily dosage 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.

After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, ALDACTONE may be administered in doses of 100 to 400 mg daily in preparation

for surgery. For patients who are considered unsuitable for surgery, ALDACTONE may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

Malignant Hypertension: ALDACTONE 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: ALDACTONE 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 to 200 mg daily in divided doses is usual however 50 mg daily 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.

ALDACTONE may be administered continuously or as a cyclical dosage for approximately three weeks out of every four. Dosing from day 5 to 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.

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## **CONTRAINDICATIONS**

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Acute renal insufficiency, significant impairment of renal function, anuria, Addison's disease, hyperkalaemia, pregnancy, hypersensitivity to spironolactone or with concomitant use of eplerenone.

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## **WARNINGS AND PRECAUTIONS**

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

Hyperkalemia may be fatal in patients with Severe Heart Failure (NYHA Class III-IV). Potassium and creatinine levels should be closely monitored one 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 > 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 for serum creatinine > 4 mg/dL.

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.

Periodic estimation of serum electrolytes is desirable due to the possibility of hyperkalaemia, hyponatraemia and possible transient 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.

Spironolactone should be considered for hirsutism only after other possible measures have been explored and should not be prescribed for hirsutism in women of reproductive age unless appropriate steps are taken to prevent conception while taking ALDACTONE.

## **Pregnancy and Lactation**

Spironolactone is contraindicated for use during pregnancy. Women of reproductive age should take appropriate steps to prevent conception.

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.

## **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.

## **Other**

Animal Studies: - 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 20-250 mg/kg daily for up to 52 weeks.

In a two year oral carcinogenicity study in which rats were administered 10, 30, 100, 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.

Spirolactone 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 one year. In one long-term (two-year) oral carcinogenicity study of potassium canrenoate in the rat, 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.

Spirolactone was devoid of teratogenic effects in mice (0-20 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 vesical weights in males; increased luteinizing hormone secretion and ovarian and uterine weights in females) were reported in one study at doses of approximately 50 and 100 mg/kg/day. Feminisation of the external genitalia of male foetuses was reported in another study in rats at doses of approximately 200 mg/kg/day.

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## **ADVERSE EFFECTS**

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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 and duration of therapy and is normally reversible when ALDACTONE is discontinued. In rare instances some breast enlargement may persist.

Other adverse reactions that have been reported in association with ALDACTONE are: gastrointestinal symptoms including cramping, diarrhoea, nausea, vomiting, gastric bleeding, ulceration and gastritis; drowsiness, malaise, dizziness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, leucopenia (including agranulocytosis), thrombocytopenia, abnormal hepatic function, electrolyte disturbances, hyperkalemia, leg cramps, alopecia, hypertrichosis, pruritus, rash, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, changes in libido, benign breast neoplasm, breast pain, menstrual disorders,

including irregular menses or amenorrhoea, and post-menopausal bleeding, and acute renal failure.

Adverse reactions are usually reversible upon discontinuation of the drug.

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## **INTERACTIONS**

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

ALDACTONE potentiates the effects of other diuretics and antihypertensives given concomitantly. The dose of such drugs may need to be reduced when ALDACTONE is added to the treatment regimen.

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

Aspirin attenuates the diuretic effect of spironolactone by blocking the secretion of canrenone in the renal tubule. Indomethacin and mefenamic acid have been shown to inhibit the excretion of canrenone.

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

Spironolactone enhances the metabolism of antipyrine.

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.

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

### **Effect on laboratory tests**

Several reports of possible interference with digoxin radioimmunoassays by spironolactone, or its metabolites have appeared in the literature. Neither the extent nor the potential clinical significance of its interference (which may be assay-specific) has been fully established.

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## **OVERDOSAGE**

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Overdosage may be manifested by nausea and vomiting 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.

Symptomatic and supportive measures should be employed. There is no specific antidote. Treat fluid depletion, electrolyte imbalances, and hypotension by established procedures.

Hyperkalaemia can be treated promptly by the rapid intravenous administration of glucose (20 to 50 percent) 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.

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

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## **PHARMACEUTICAL PRECAUTIONS**

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Store below 30°C.

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## **MEDICINE CLASSIFICATION**

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Prescription Medicine

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## **PACKAGE QUANTITIES**

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ALDACTONE 25 mg - blister packs of 100 Tablets

ALDACTONE 100 mg - blister packs of 100 Tablets

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## **FURTHER INFORMATION**

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Nil

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**NAME AND ADDRESS OF DISTRIBUTOR**

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Pfizer New Zealand Ltd  
PO Box 3998  
Auckland, New Zealand

Toll Free number: 0800 736 363

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**DATE OF PREPARATION**

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19 May 2010.