SPIRONOLACTONE

ALDACTONE®

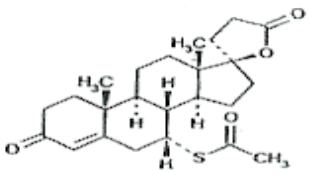
25 mg, 50 mg and 100 mg FILM-COATED TABLET

1.0 PHARMACOLOGIC CATEGORY

Diuretic/Antihypertensive.

2.0 DESCRIPTION

$C_{24}H_{32}O_4S$. 416.57 (1) Pregn-4-ene-21-carboxylic acid, 7-(acetylthio)-17-hydroxy-3-oxo-, γ-lactone (7α,17α)-; (2) 17-Hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone acetate.



Spironolactone contains not less than 97.0 percent and not more than 103.0 percent of $C_{24}H_{32}O_4S$, calculated on the dried basis.

3.0 FORMULATION/COMPOSITION

Spironolactone (Aldactone) 25 mg Tablet: Each film-coated tablet contains 25 mg spironolactone.

Spironolactone (Aldactone) 50 mg Tablet: Each film-coated tablet contains 50 mg spironolactone.

Spironolactone (Aldactone) 100 mg Tablet: Each film-coated tablet contains 100 mg spironolactone.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Spironolactone is indicated for the following:

1. Essential hypertension.
2. Short-term pre-operative treatment of patients with primary hyperaldosteronism.
3. Establishing a diagnosis of primary hyperaldosteronism.

4. Congestive heart failure (alone or in combination with standard therapy), including severe heart failure (New York Heart Association [NYHA] Class III-IV) to increase survival and reduce the risk of hospitalization when used in addition to standard therapy.
5. Conditions in which secondary hyperaldosteronism may be present, including liver cirrhosis accompanied by edema and/or ascites, nephrotic syndrome, and other edematous conditions (alone or in combination with standard therapy).
6. Diuretic-induced hypokalemia/hypomagnesemia as adjunctive therapy.
7. Management of hirsutism.

4.2 Dosage and Method of Administration

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/day to 100 mg/day, which for difficult or severe cases may be gradually increased at intervals of 2 weeks up to 200 mg/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 spironolactone 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)

Based on the Randomized Aldactone Evaluation Study (RALES), treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg once daily in patients with a serum potassium ≤5.0 mEq/L and serum creatinine ≤2.5 mg/dL. 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 Special Warnings and Precautions for Use: Hyperkalemia 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 mg/day to 400 mg/day. Maintenance dose should be individually determined.

Nephrotic Syndrome

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

Edema in Children

Initial dosage is 3 mg/kg body weight daily in divided doses. Dosage should be adjusted on the basis of response and tolerance. If necessary, a suspension may be prepared by pulverizing spironolactone tablets with a few drops of glycerin and adding cherry syrup. Such a suspension is stable for 1 month when refrigerated.

Diagnosis and Treatment of Primary Hyperaldosteronism

Spironolactone 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 hypokalemia and 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 Spironolactone administration, but drops when Spironolactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

Short-Term Pre-operative Treatment of Primary Hyperaldosteronism

After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, spironolactone 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, spironolactone may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

Hypokalemia/Hypomagnesemia

25 mg to 100 mg daily may be useful in treating diuretic-induced hypokalemia and/or hypomagnesemia when oral potassium and/or magnesium supplements are considered inappropriate.

Management of Hirsutism

The usual dose is 100 mg/day to 200 mg/day, preferably in divided dose.

4.3 Contraindications

Spironolactone is contraindicated in patients with the following:

- Acute renal insufficiency, significant renal compromise, anuria
- Addison's disease
- Hyperkalemia
- Hypersensitivity to spironolactone
- Concomitant use of eplerenone

4.4 Special Warnings and Precautions for Use

Concomitant use of spironolactone with other potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin, or other drugs or conditions known to cause hyperkalemia, potassium supplements, a diet rich in potassium or salt substitutes containing potassium, may lead to severe hyperkalemia.

Periodic estimation of serum electrolytes is recommended due to the possibility of hyperkalemia, hyponatremia and possible transient blood urea nitrogen (BUN) elevation, especially in the elderly and/or in patients with pre-existing impaired renal or hepatic function.

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.

Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even when renal function is normal.

Hyperkalemia in Patients with Severe Heart Failure

Hyperkalemia may be fatal. It is critical to monitor and manage serum potassium in patients with severe heart failure receiving spironolactone. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium >3.5 mEq/L. The recommended monitoring for potassium and creatinine is 1 week after initiation or increase in dose of spironolactone, monthly for the first 3 months, then quarterly for a year, and then every 6 months. Discontinue or interrupt treatment for serum potassium >5 mEq/L or for serum creatinine >4 mg/dL (see section **4.2 Dosage and Method of Administration: Severe heart failure in conjunction with standard therapy (NYHA Class III-IV)**).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Concomitant use of drugs known to cause hyperkalemia with spironolactone may result in severe hyperkalemia.

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

Spironolactone reduces vascular responsiveness to norepinephrine. Caution should be exercised in the management of patients subjected to anesthesia while they are being treated with spironolactone.

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

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.

Spironolactone can interfere with assays for plasma digoxin concentrations.

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

Coadministration of spironolactone with carbenoxolone may result in decreased efficacy of either agent.

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

Spironolactone may reduce mitotane plasma levels in adrenocortical carcinoma patients and should not be used concomitantly.

Like other diuretics, spironolactone reduces the renal clearance of lithium, thus increasing the risk of lithium toxicity. Monitor lithium levels periodically when spironolactone is coadministered.

4.6 Fertility, Pregnancy and Lactation

Spironolactone was devoid of teratogenic effects in mice. Rabbits receiving spironolactone showed reduced conception rate, increased resorption rate, and lower number of live births. No embryotoxic effects were seen in rats administered high dosages, but limited, dosage-related hypoprolactinemia and decreased ventral prostate and seminal vesicle weights in males, and increased luteinizing hormone secretion and ovarian and uterine weights in females were reported. Feminization of the external genitalia of male fetuses was reported in another study in rats.

There are no studies in pregnant women. Spironolactone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Canrenone, a major (and active) metabolite of spironolactone, appears in human breast milk. Because many drugs are excreted in human milk and because of the unknown potential for adverse effects on the breast-feeding infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on Ability to Drive and Use Machines

See section **4.4 Special Warnings and Precautions for Use**.

4.8 Undesirable Effects

The following adverse events have been reported in association with spironolactone therapy:

Table 1. Adverse Drug Reactions	
System Organ Class	**Adverse Drug Reactions**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Benign breast neoplasm (male)
Blood and lymphatic system disorders	Agranulocytosis, Leukopenia, Thrombocytopenia
Metabolism and nutrition disorders	Hyperkalemia, Electrolyte imbalance
Psychiatric disorders	Confusional state, Libido disorder
Nervous system disorders	Dizziness
Gastrointestinal disorders	Nausea, Gastrointestinal disorder
Hepatobiliary disorders	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Pruritus, Rash, Urticaria, Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Drug reaction with eosinophilia and systemic symptoms (DRESS) , Alopecia, Hypertrichosis.
Musculoskeletal and connective tissue disorders	Muscle spasms
Renal and urinary disorders	Acute kidney injury
Reproductive system and breast disorders	Gynecomastia, Breast pain (male), Menstrual disorder, Breast pain (female)
General disorders and administration site conditions	Malaise

4.9 Overdose and Treatment

Acute overdose may be manifested by nausea, vomiting, drowsiness, mental confusion, maculopapular or erythematous rash, or diarrhea. Electrolyte imbalance and dehydration may occur. There is no specific antidote. Spironolactone use should be discontinued and potassium intake (including dietary sources) restricted.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 drug by this mechanism. It may be given alone or with other diuretic agents that act more proximally in the renal tubule.

Aldosterone Antagonist Activity

Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for edema and ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active diuretic therapy.

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.

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

Severe Heart Failure

RALES was a multinational, double-blind study in 1663 patients with an ejection fraction of ≤35%, a history of NYHA Class IV heart failure within 6 months, and Class III-IV heart failure at the time of randomization. All patients were required to be taking a loop diuretic and, if tolerated, an ACE inhibitor. 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 significant mortality benefit detected on a planned interim analysis. Spironolactone reduced the risk of death by 30% compared to placebo ($p < 0.001$; 95% confidence interval 18%-40%). Spironolactone reduced the risk of cardiac death, primarily sudden death and death from progressive heart failure by 31% compared to placebo ($p < 0.001$; 95% confidence interval 18%-42%).

Spironolactone also reduced the risk of hospitalization for cardiac causes (defined as worsening heart failure, angina, ventricular arrhythmias or myocardial infarction) by 30% ($p < 0.001$; 95% confidence interval 18%-41%). Changes in NYHA class were more favorable with spironolactone: in the spironolactone group, NYHA class at the end of the study improved in 41% of patients and

worsened in 38% compared to improved in 33% and worsened in 48% in the placebo group (p <0.001).

5.2 Pharmacokinetic Properties

Spironolactone is rapidly and extensively metabolized. Sulfur-containing products are the predominant metabolites and are thought to be primarily responsible, together with spironolactone, for the therapeutic effects of the drug. 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) Post-Steady-State Half-Life**
7-α-(thiomethyl) spirolactone	1.25	391 ng/mL at 3.2 hours	13.8 hours (6.4) (terminal)
6-ß-hydroxy-7-α-(thiomethyl) spirolactone	1.50	125 ng/mL at 5.1 hours	15.0 hours (4.0) (terminal)
Canrenone	1.41	181 ng/mL at 4.3 hours	16.5 hours (6.3) (terminal)
Spironolactone	1.30	80 ng/mL at 2.6 hours	Approximately 1.4 hours (0.5) (β half-life)

The pharmacological activity of spironolactone metabolites in man is not known. However, in adrenalectomized rats, the antimineralocorticoid activities of the metabolites canrenone (C), 7-α-(thiomethyl) spirolactone (TMS), and 6-β-hydroxy-7-α-(thiomethyl) spirolactone (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 nine healthy, drug-free volunteers. Food increased the bioavailability of

unmetabolized spironolactone by almost 100%. The clinical importance of this finding is not known.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Orally administered spironolactone has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150 and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In 24-month studies in which rats were administered doses of about 10, 30, 100 and 150 mg/kg/day of spironolactone, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant increase in benign uterine endometrial stromal polyps in females.

A dose-related (above 30 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, canrenone, is also a major product of spironolactone in man) for a period of 1 year. In 2-year studies in the rats, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular and mammary tumors.

Neither spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither spironolactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests *in vitro.* In the presence of metabolic activation, spironolactone has been reported to be negative in some mammalian mutagenicity tests *in vitro* and inconclusive (but slightly positive) for mutagenicity in other mammalian tests *in vitro.* In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian tests *in vitro,* inconclusive in others, and negative in still others.

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg/kg/day of spironolactone, there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. When injected into female rats (100 mg/kg/day for 7 days, i.p.), spironolactone was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a 2-week post-treatment observation period. These effects were associated with retarded ovarian follicle development and a reduction in circulating estrogen levels, which would be expected to impair mating, fertility and fecundity. Spironolactone (100 mg/kg/day), administered i.p. to female mice during a 2-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became

pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg, also increased the latency period to mating.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry.

6.2 Storage Condition(s)

Store at temperatures not exceeding 30°C.

6.3 Availability

Spironolactone (Aldactone) 25 mg Tablets: Round, buff colored, biconvex film-coated tablet engraved SEARLE over 39 on one side and plain on the other. Peppermint odor. Blister pack of 10 tablets (Box of 100's).

Spironolactone (Aldactone) 50 mg Tablets: Round, white, biconvex film-coated tablets, plain on one side and engraved SEARLE over 916 on the other. Peppermint odor. Blister pack of 10 tablets (Box of 100's).

Spironolactone (Aldactone) 100 mg Tablets: Round, white, biconvex, film-coated tablets engraved SEARLE over 134 on one side and plain on the other. Peppermint odor. Blister pack of 10 tablets (Box of 100's)

7.0 FDA REGISTRATION NUMBER

25 mg Tablet: DRP-2016
50 mg Tablet: DRP-2013
100 mg Tablet: DRP-2014

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

25 mg Tablet: 15 July 1975
50 mg Tablet: 16 Sept 1983
100 mg Tablet: 15 May 1980

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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