DESCRIPTION

Aldactone oral tablets contain 25 mg, 50 mg, or 100 mg of the aldosterone antagonist spironolactone, 17-hydroxy-7α-mercapto-3-oxo-17β-pregn-4-ene-21-carboxylic acid γ-lactone acetate, which has the following structural formula:

![Structural formula of spironolactone](image)

Spironolactone is practically insoluble in water, soluble in alcohol, and freely soluble in benzene and in chloroform.

Inactive ingredients include calcium sulfate, corn starch, flavor, hypromellose, iron oxide, magnesium stearate, polyethylene glycol, povidone, and titanium dioxide.

ACTIONS / CLINICAL PHARMACOLOGY

Mechanism of action: 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 causes increased amounts of sodium and water to be excreted, while potassium is retained. Aldactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents which 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 the nephrotic syndrome. By competing with aldosterone for receptor sites, Aldactone provides effective therapy for the edema and ascites in those conditions. Aldactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active diuretic therapy.

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 antagonizing 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.

Pharmacokinetics: 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 (Aldactone film-coated tablets) daily for 15 days. On the 15th day, spironolactone was given immediately after a low-fat breakfast and blood was drawn thereafter.

<table>
<thead>
<tr>
<th>Accumulation Factor:</th>
<th>AUC (0-24 hr, day 15)/AUC (0-24 hr, day 1)</th>
<th>Mean Peak Serum Concentration</th>
<th>Mean (SD) Post-Steady State Half-Life</th>
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</thead>
<tbody>
<tr>
<td>7-α-(thiomethyl) spirolactone (TMS)</td>
<td>1.25</td>
<td>391 ng/mL at 3.2 hr</td>
<td>13.8 hr (6.4) (terminal)</td>
</tr>
<tr>
<td>6-ß-hydroxy-7-α-(thiomethyl) spirolactone (HTMS)</td>
<td>1.50</td>
<td>125 ng/mL at 5.1 hr</td>
<td>15.0 hr (4.0) (terminal)</td>
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<tr>
<td>Canrenone (C)</td>
<td>1.41</td>
<td>181 ng/mL at 4.3 hr</td>
<td>16.5 hr (6.3) (terminal)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>1.30</td>
<td>80 ng/mL at 2.6 hr</td>
<td>Approximately 1.4 hr (0.5) (ß half-life)</td>
</tr>
</tbody>
</table>

The pharmacological activity of spironolactone metabolites in man is not known. However, in the adrenalectomized 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
Aldactone
spironolactone tablets, USP

Aldactone (spironolactone) is indicated in the management of:

Primary hyperaldosteronism for:

- Establishing the diagnosis of primary hyperaldosteronism by therapeutic trial.
- 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.

Long-term maintenance therapy for patients with bilateral micro- or macronodular adrenal hyperplasia (idiopathic hyperaldosteronism).

Edematous conditions for patients with:

- Congestive heart failure: For the management of edema and sodium retention when the patient is only partially responsive to, or is intolerant of, other therapeutic measures. Aldactone is also indicated for patients with congestive heart failure taking digitalis where the cardiovascular response is inadequate with other agents.
- Chronic renal failure, whether or not accompanied by edema and/or ascites: Aldosterone levels may be exceptionally high in this condition. Aldactone is indicated for maintenance therapy together with bed rest and the restriction of fluid and sodium.

The nephrotic syndrome: For nephrotic patients when treatment of the underlying disease, restriction of fluid and sodium intake, and the use of other diuretics do not provide an adequate response.

Essential hypertension

Usually in combination with other drugs. Aldactone is indicated for patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate.

Hypokalemia

For the treatment of patients with hypokalemia when other measures are considered inappropriate or inadequate. Aldactone is also indicated for the restriction of the prophylaxis of hypokalemia in patients taking digitalis when other measures are considered inadequate or inappropriate.

Usage in Pregnancy

The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not provide adequate control of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is unsupported and unnecessary. There is hypervolemia during normal pregnancy, which is not harmful to either the fetus or the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recurrence will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

Aldactone is contraindicated for patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, or hyperkalemia.

WARNINGS

Potassium supplements may be given in the form of medication or as a diet rich in potassium, should not ordinarily be given in association with Aldactone therapy. Excessive potassium intake may cause hyperkalemia in patients receiving Aldactone (see Precautions: General). Aldactone should be administered cautiously with other potassium-sparing diuretics. Aldactone, when used with ACE inhibitors or indomethacin, even in the presence of a diuretic, has been associated with severe hyperkalemia. Extreme caution should be exercised when Aldactone is given concomitantly with these drugs. Aldactone should be used with caution in patients with impaired hepatic function because a change in the ratio of fluid and electrolyte balance may precipitate hepatic coma.

Lithium generally should not be given with diuretics (see Precautions: Drug interactions).

PRECAUTIONS

General: All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance, eg, hypomagnesemia, hypokalemia, hypochloremic alkalosis, and hyperkalemia.

Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of the mouth, thirst, weakness, lassitude, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities, which may be fatal. Consequently, no potassium supplement should ordinarily be given with Aldactone.

Concomitant administration of potassium-sparing diuretics and ACE inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs), eg, indomethacin, has been associated with severe hyperkalemia. If hyperkalemia is suspected (warning signs include paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock) the electrocardiogram (ECG) should be obtained. However, it is important to monitor serum potassium levels because aldosterone hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, Aldactone should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These include the intravenous administration of 5% or 10% sodium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose and insulin with a rapid-acting insulin preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dialysis.

Reversible hyperchloremic metabolic acidosis, usually in association with hyperkalemia, has been reported to occur in some patients with decompensated heart failure and shock, even in the presence of normal renal function.

Dilutional hyponatremia, manifested by dryness of the mouth, thirst, lassitude, and drowsiness, and confirmed by a low serum sodium level, may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics, and dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than the oral or rectal administration of sodium, except in rare instances when the hypoaldosteronism is life-threatening.

Aldactone therapy may cause a transient elevation of BUN, especially in patients with preexisting renal impairment. Aldactone may cause mild acidosis.

Gynecomastia may develop in association with the use of spironolactone; physicians should be alert to this possible onset. The development of gynecomastia 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 when Aldactone is discontinued.

Information for Patients: Patients who receive Aldactone should be advised to avoid potassium supplements and foods containing high levels of potassium including salt substitutes.

Laboratory tests: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals, particularly in the elderly and those with significant renal or hepatic impairments.

Drug interactions:

ACE inhibitors: Concomitant administration of ACE inhibitors with potassium-sparing diuretics has been associated with severe hyperkalemia.

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia, may occur.

Pressor amines (eg, norepinephrine): Spironolactone reduces the vascular responsiveness to norepinephrine. Therefore, caution should be exercised in the management of patients subjected to regional or general anesthesia while they are being treated with Aldactone.

Skeletal muscle relaxants, nondopaminergic (eg, tubocurarine): Possible increased responsiveness to the muscle relaxant may result.

Lithium: Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Nonsteroidal anti-inflammatory drugs (NSAIDs): In some patients, the administration of an NSAID can
reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing and thiazide diuretics. Combination of NSAIDs, eg, indomethacin, with potas- sium-sparing diuretics has been associated with severe hyperkalemia. Therefore, when Aldactone and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

**Digoxin:** Spironolactone has been shown to increase the half-life of digoxin and may result in increased serum digoxin levels and subsequent digitalis toxicity. It may be necessary to reduce the maintenance and digitalization doses when spironolactone is administered, and the patient should be carefully monitored to avoid over- or undigitalization.

**Drug/Laboratory test interactions:** Several reports of possible interference with digoxin radioimmunoassays by spironolactone and its metabolite, canrenoate, have been reported in the literature. Neither the extent nor the potential clinical significance of its interference (which may be assay-spe- cific) has been fully established.

**Carcinogenesis, mutagenesis, impairment of fertility:** Oral administration of potassium canrenoate has been shown to be tumorigenic in dietary administration studies performed in rats, with its proliferative effects manifested at doses when spironolactone is administered, and the range of proliferative effects included significant increases in hepatocellular adenomas of the thyroid and testes and, in male rats, a dose-related increase in benign uterine endometrial stromal polyps in females. A dose-related incidence (20 mg/kg/day) of mye- locytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, can- renone, is also a major product of spironolactone in man) for a period of one year. In two-year studies in the rat, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thy- roid, testicular and mammary tumors.

Neither spironolactone nor potassium canrenoate pro- duces tumors in tests using bacteria or yeast. In the absence of metabolic activation, neither spirono- lactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests in vivo. In the presence of metabolic activation, spironolactone has been re- ported to be negative in some mammalian mutagenici- ties in vitro and inconclusive (but slightly positive) in other, and inconclusive (but slightly positive) in still others.

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg spironolac- tone/kg/day, there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups when administered to pregnant female rats (10 mg/kg/day for 7 days, i.p.), spironolactone was found to induce a reduction in the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a two-week posttreatment 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 two-week co- habitation 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/day, increased the la- tent period to mating.

**Preparation of pregnant women requires that the anticipated benefit be weighed against the possible hazards to the fetus. If use of the drug is deemed essential, an alternative method of infant feed-ing should be instituted.**

**Pediatric use:** Safety and effectiveness in pediatric pa- tients has not been established.

**ADVERSE REACTIONS**

The following adverse reactions have been reported and, within each category (body system), are listed in order of decreasing severity.

**Digestive:** Gastric bleeding, ulceration, gastritis, diarrhea and cramping, nausea, vomiting.

**Endocrine:** Gynecomastia. Excitation (Precautions), inability to achieve or maintain erection, irregular menses or amen- orrhea, postmenopausal bleeding. Carcinoma of the breast has been reported in patients taking spirono- lactone but a cause and effect relationship has not been es- tablished.

**Hematologic:** Agranulocytosis.

**Hypersensitivity:** Fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reac- tions, vasculitis.

**Nervous system/psychiatric:** Mental confusion, ataxia, headache, drowsiness, lethargy, restlessness.

**Liver / biliary:** A very few cases of mixed cholestatic/ hepatocellular toxicity, with one reported fatality, have been reported with spironolactone administration. Liver toxicity is associated with increased serum aminotransferases and alkaline phosphatase.

**Renal:** Renal dysfunction (including renal failure).

**OVERDOSAGE**

The oral LD₅₀ of spironolactone is greater than 1,000 mg/kg in mice, rats, and rabbits. Acute overdose of spironolactone may be mani- fested by drowsiness, mental confusion, maculopapular or erythematosus rash, nausea, vomiting, dizziness, or di- seases. Rarely, instances of hyperkalemia, hyperkalemia, or hepatic coma may occur in patients with severe liver disease, but these are unlikely due to acute overdosage. Hyperkalemia may occur, especially in patients with im- paired renal function.

**Treatment:** Induce vomiting or evacuate the stomach by lavage. There is no specific antidote. The use of a cathartic is sup- portive to maintain hydration, electrolyte balance, and vital function.

Patients who have renal impairment may develop spironolactone-induced hyperkalemia. In such cases, Al- dactone should be discontinued immediately. On rechallenge with severe hyperkalemia, the clinical situation dictates the procedures to be employed. These include the intra- venous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or par- enteral administration of glucagon. If, after repeated hyperkalemia preparation. These are temporary measures to be repeated as required. Cationic exchange resins such as sodium polystyrene sulfonate may be orally or rectally administered. Persistent hyperkalemia may require dial-ysis.

**DOSEAGE AND ADMINISTRATION**

**Primary hyperaldosteronism.** Aldactone may be em- ployed as an initial diagnostic measure to provide pre- sumptive 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 hyper- kalemia and of hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteron- ism. For patients with hypertension resistant to diuretics, the dose is gradually increased to the lowest effective dosage determined for the individual patient.

**Short test:** Aldactone is administered at a daily dosage of 400 mg for four days. If serum potassium increas- es during Aldactone administration but drops when Al- dactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered. After the diagnosis of primary hyperaldosteronism is established by more definitive testing procedures, Al- dactone may be administered in doses of 100 to 400 mg daily in preparation for surgery. For patients with mild to moderate hyperkalemia who are considered unsuitable for surgery, Aldactone may be employed for long-term maintenance in doses according to the lowest effective dosage determined for the individual patient.

**Edema in adults (congestive heart failure, hepatic cir- rhosis, or nephrotic syndrome).** An initial daily dosage of 100 mg of Aldactone administered in either single or divided doses is recommended, but may range from 25 to 200 mg daily. When given as the sole agent for di- uresis, Aldactone should be continued for at least five days at the initial dosage level, after which it may be ad- justed to the optimal therapeutic or maintenance level administered in either single or divided daily doses. If,
after five days, an adequate diuretic response to Aldactone has not occurred, a second diuretic which acts more proximally in the renal tubule may be added to the regimen. Because of the additive effect of Aldactone when administered concurrently with such diuretics, an enhanced diuresis usually begins on the first day of combined treatment; combined therapy is indicated when more rapid diuresis is desired. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

**Essential hypertension.** For adults, an initial daily dosage of 50 to 100 mg of Aldactone administered in either single or divided doses is recommended. Aldactone may also be given with diuretics which act more proximally in the renal tubule or with other antihypertensive agents. Treatment with Aldactone should be continued for at least two weeks, since the maximum response may not occur before this time. Subsequently, dosage should be adjusted according to the response of the patient.

**Hypokalemia.** Aldactone in a dosage ranging from 25 mg to 100 mg daily is useful in treating a diuretic-induced hypokalemia, when oral potassium supplements or other potassium-sparing regimens are considered inappropriate.

**HOW SUPPLIED**

Aldactone 25-mg tablets are round, light yellow, film coated, with SEARLE and 1001 debossed on one side and ALDACTONE and 25 on the other side, supplied as:

<table>
<thead>
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<th>NDC Number</th>
<th>Size</th>
</tr>
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<tbody>
<tr>
<td>0025-1001-31</td>
<td>bottle of 100</td>
</tr>
<tr>
<td>0025-1001-51</td>
<td>bottle of 500</td>
</tr>
<tr>
<td>0025-1001-55</td>
<td>bottle of 2500</td>
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</table>

Aldactone 50-mg tablets are oval, light orange, scored, film coated, with SEARLE and 1041 debossed on the scored side and ALDACTONE and 50 on the other side, supplied as:

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<th>Size</th>
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<tr>
<td>0025-1041-31</td>
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<td>0025-1041-34</td>
<td>carton of 100 unit dose</td>
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Aldactone 100-mg tablets are round, peach colored, scored, film coated, with SEARLE and 1031 debossed on the scored side and ALDACTONE and 100 on the other side, supplied as:

<table>
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<tbody>
<tr>
<td>0025-1031-31</td>
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<tr>
<td>0025-1031-34</td>
<td>carton of 100 unit dose</td>
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</tbody>
</table>

Store below 77°F (25°C).