Aldactazide®
spironolactone and hydrochlorothiazide tablets

**WARNING**

Spironolactone, a component of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see Precautions). Aldactazide should be used only in those conditions described under Indications and Usage. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static but must be reevaluated as conditions in each patient warrant.

**DESCRIPTION**

Aldactazide oral tablets contain:

- hydrochlorothiazide . . . . . . . . . . . . . . . . 25 mg
- spironolactone . . . . . . . . . . . . . . . . . . 25 mg

Aldactazide® tablets contain:

- hydrochlorothiazide . . . . . . . . . . . . . . . . 50 mg
- spironolactone . . . . . . . . . . . . . . . . . . . 50 mg

Spironolactone (Aldactone®), an aldosterone antagonist, is 17-hydroxy-7-α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone acetate and has the following structural formula:

![Chemical Structure of Spironolactone](image1)

Hydrochlorothiazide is slightly soluble in water and freely soluble in benzene and in chloroform.

**Mechanism of action:** Aldactazide is a combination of two diuretic agents with different but complementary mechanisms and sites of action, thereby providing additive diuretic and antihypertensive effects. Additionally, the spironolactone component helps to minimize the potassium loss characteristically induced by the thiazide component.

The diuretic effect of spironolactone is mediated through its action as a specific pharmacologic antagonist of aldosterone, primarily by competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Hydrochlorothiazide promotes the excretion of sodium and water primarily by inhibiting their reabsorption in the cortical diluting segment of the distal renal tubule.

Aldactazide is effective in significantly lowering the systolic and diastolic blood pressure in many patients with essential hypertension, even when aldosterone secretion is within normal limits.

Both spironolactone and hydrochlorothiazide reduce exchangeable sodium, plasma volume, body weight, and blood pressure. The diuretic and antihypertensive effects of the individual components are potentiated when spironolactone and hydrochlorothiazide are given concurrently.

**Pharmacokinetics:** Spironolactone is rapidly and extensively metabolized. Sulfur-containing products are the predominant metabolites and are thought to be primarily responsible, to a lesser extent, 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.

**INDICATIONS AND USAGE**

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see Precautions section). Aldactazide should be used only in those conditions described below. Unnecessary use of this drug should be avoided. Aldactazide is indicated for:

### Edematous conditions

- Essential hypertension
- Edematous conditions
- Congestive heart failure
- Cirrhosis of the liver accompanied by edema and/or ascites
- Nephrotic syndrome

The nephrotic syndrome:

- For nephritic 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

For patients with essential hypertension in whom other measures are considered inadequate or inappropriate.

The nephrotic syndrome:

- For nephritic 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

For patients with essential hypertension in whom other measures are considered inadequate or inappropriate.

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If hyperkalemia is suspected (warning signs include paresthesia, muscle weakness, fatigue, flaccid paralysis of the extremities, bradycardia and shock) an electrocardiogram (ECG) should be obtained. However, it is important to moni-
tor serum potassium levels, since mild hyperkalemia may not be associated with ECG changes.

If hyperkalemia is present, Aldactazide should be discontinued immediately. With se-
vere hyperkalemia, the clinical situation dictates the procedures to be employed. These include
the intravenous administration of calcium chlo-
ride solution, sodium bicarbonate solution, and
/or the oral or parenteral administration of
sodium thiosulfate in a dose of 20-40 g (admin-
istered slowly). Potassium chlo-
ride may induce signs of digitalis intoxica-
tion at previously tolerated dosage levels. Al-
though any chloride deficit is generally mild
and usually does not require specific treatment
except under extraordinary circumstances (as in
liver disease or renal disease), chloride re-
placement may be required in the treatment of
metabolic alkalosis.

Aldactazide therapy may cause a transient
increase in BUN. This appears to represent a
concentration phenomenon rather than renal
toxicity, since the BUN level returns to normal
after use of Aldactazide is discontinued. Pro-
gressive elevation of BUN is suggestive of the
presence of preexisting renal impairment.

Reversible hyperchloremic metabolic acido-
sis, usually in association with hyperkalemia,
has been reported to occur in some patients
with decompensated hepatic cirrhosis, even in
the presence of normal renal function.

Dilutional hyponatremia, manifested by dry-
ness of the mouth, thirst, lethargy, and drows-
iness, and confirmed by a low serum sodium
level, may be induced, especially when Aldac-
tazide is administered in combination with
other diuretics, and dilutional hyponatremia
may occur in edematous patients in hot weath-
ner; appropriate therapy is water restriction
rather than administration of sodium, except in
rare instances when the hyponatremia is life-
threatening. A true low-salt syndrome may
rarely develop with Aldactazide therapy and
may be manifested by increasing mental con-
fusion similar to that observed with hepatic
coma. This syndrome is differentiated from di-
lutional hyponatremia in that it does not occur
with obvious fluid retention. Its treatment re-
quires that diuretic therapy be discontinued
and sodium administered.

Hyperuricemia may occur or acute gout may
be precipitated in patients receiving thi-
azide diuretics. Thiazide diuretics, together with acidosis, may increase the urinary excretion of magnesium; this may result in hypomagnesemia. Increases in cho-

lsterol and triglyceride levels may be associ-
ated with thiazide diuretic therapy.

In diabetic patients, dosage adjustments of
oral or insulin-glycemic agents may be
required. Hyperglycemia may occur with th-
iazide diuretics. Thus, latent diabetes mellitus
can be manifested by increasing mental con-
fusion similar to that observed with hepatic
coma. This syndrome is differentiated from di-
lutional hyponatremia, usually in association with hyperkalemia, has been reported to occur in some patients
with decompensated hepatic cirrhosis, even in
the presence of normal renal function.

Aldactazide is contraindicated in patients with
anuria, acute renal insufficiency, significant im-
pairment of renal excretory function, or hyper-
kalemia, and in patients who are allergic to thi-
zide diuretics or to other sulfonamide-derived
drugs. Aldactazide may also be contraindicated
in acute or severe hepatic failure.

WARNINGS

Potassium supplementation, either in the form of medications or as a diet rich in potassium, should not ordinarily be given in association with Aldactazide therapy. Excessive potassium intake may cause hyperkalemia in patients re-
ceiving Aldactazide (see Precautions: General). Aldactazide should not be administered con-
comitantly with other potassium-sparing diuret-
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Aldactazide is discontinued. In rare instances some breast enlargement may persist when Aldactazide is discontinued.

Information for patients: Patients who receive Aldactazide 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. Antidiabetic drugs (eg, oral agents, insulin): Dosage adjustment of the antidiabetic drug may be required. Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hyperkalemia, may occur. Presor amines (eg, norepinephrine): Both spironolactone and hydrochlorothiazide reduce 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 Aldactazide. Skeletal muscle relaxants, nondepolaring (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 potassium-sparing diuretics has been associated with severe hyperkalemia. Therefore, when Aldactazide 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. This 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 underdigitalization. Drug/Laboratory test interactions: Thiazides should be discontinued before carrying out tests for parathyroid function (see Precautions: General). Thiazides may also decrease serum PBI levels without evidence of alteration of thy- roid function. 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. Carcinogenesis, mutagenesis, impairment of fertility: Spironolactone: 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 hepatocyte nodules and hyperplastic nodules). In a 24-month study in which the same strain of rat was administered doses of about 10, 30, 100 and 150 mg spironolactone/kg/day, 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, but not dose-related, increase in benign uterine endometrial stromal polyps in females. A dose-related (above 20 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 one year. In two year studies in the rat, 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, spirono- lactone 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 reproductive study in which female rats received dietary doses of 15 and 50 mg spironolactone/kg/day, 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 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. Spi- ronolactone (100 mg/kg/day), administered up to female mice during a two week cohabitation period with untreated males, decreased the number of mated females that conceived (effect shown to be caused by an inhibition of ovula- tion) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of im- plantation), and at 200 mg/kg, also increased the latency period to mating. Hydrochlorothiazide: Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approxi- mately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogen- icity in male mice. Hydrochlorothiazide was not genotoxic in in vitro assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of Salmonella typhimurium (Ames assay) and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in in vivo assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and Drosophila sex-linked recessive lethal trait gene. Posi- tive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clasto- genicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1900 µg/ml, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration. Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation. Pregnancy: Teratogenic effects. Pregnancy Cat- egory C. Hydrochlorothiazide: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, re- spectively, provided no evidence of harm to the fetus. There are, however, no adequate and well controlled studies in pregnant women. Spironolactone: Teratology studies with spi- ronolactone have been carried out in mice and rabbits at doses of up to 20 mg/kg/day. On a body surface area basis, this dose in the mouse is substantially below the maximum recom- mended human dose and, in the rabbit, approxi- mately the maximum recommended human dose. No teratogenic or other embryotoxic effects were observed in mice, but the 20 mg/kg dose caused an increased rate of re- sorption and a lower number of live fetuses in rabbits. Because of its anti-androgenic activity and the requirement of testosterone for male morphogenesis, spironolactone may have the potential for adversely affecting sex differenti- ation of the male during embryogenesis. When administered to rats at 200 mg/kg/day between gestation days 13 and 21 (late embryogenesis

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ADVERSE REACTIONS

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

Hydrochlorothiazide:

Body as a whole: Weakness.
Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Digestive: Pancreatitis, jaundice (intrahepatic cholestasis), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritati

Non-teratogenic effects: Spironolactone or its metabolites may, and hydrochlorothiazide does, cross the placental barrier and appear in cord blood. Therefore, the use of Aldactazide in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. The hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing mothers: Canrenone, a major (and active) metabolite of spironolactone, appears in human breast milk. Because spironolactone has been found to be tumorigenic in rats, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. If use of the drug is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric use: Safety and effectiveness in pediatric patients has not been established.

OVERDOSAGE

The oral LD50 of spironolactone is greater than 1,000 mg/kg in mice, rats, and rabbits. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

Acute overdosage of spironolactone may be manifested by drowsiness, mental confusion, maculopapular or erythematous rash, nausea, vomiting, diarrhea. Rarely, instances of hyperkalemia (less commonly seen with Aldactazide because the hydrochlorothiazide component tends to produce hypokalemia), or hepatic coma may occur in patients with severe liver disease, but these are unlikely due to acute overdosage.

However, because Aldactazide contains both spironolactone and hydrochlorothiazide, the toxic effects may be intensified, and signs of thiazide overdosage may be present. These include electrolyte imbalance such as hypokalemia and/or hyperkalemia. The potassium-sparing action of spironolactone may predominate and hyperkalemia may occur, especially in patients with impaired renal function.

Treatment: Induce vomiting or evacuate the stomach by lavage. There is no specific antidote. Treatment is supportive to maintain hydration, electrolyte balance, and vital functions.

Patients who have renal impairment may develop spironolactone-induced hyperkalemia. In such cases, Aldactazide should be discontinued immediately. With severe hyperkalemia, the clinical situation dictates the procedures to be employed. These include the intravenous administration of calcium chloride solution, sodium bicarbonate solution and/or the oral or parenteral administration of glucose 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.

DOSAGE AND ADMINISTRATION

Optimal dosage should be established by individual titration of the components (see boxed Warning).

Edema in adults (congestive heart failure, hepatic cirrhosis, or nephrotic syndrome). The usual maintenance dose of Aldactazide is 100 mg each of spironolactone and hydrochlorothiazide daily, administered in a single dose or in divided doses, but may range from 25 mg to 200 mg of each component daily depending on the response to the initial titration. In some instances it may be desirable to administer separate tablets of either Aldactone (spironolactone) or hydrochlorothiazide in addition to Aldactazide in order to provide optimal individual therapy.

The onset of diuresis with Aldactazide occurs promptly and, due to prolonged effect of the spironolactone component, persists for two to three days after Aldactazide is discontinued.

Essential hypertension. Although the dosage will vary depending on the results of titration of the individual ingredients, many patients will be found to have an optimal response to 50 mg to 100 mg each of spironolactone and hydrochlorothiazide daily, given in a single dose or in divided doses.

Concurrent potassium supplementation is not recommended when Aldactazide is used in the long-term management of hypertension or in the treatment of most edematous conditions, since the spironolactone content of Aldactazide is usually sufficient to minimize loss induced by the hydrochlorothiazide component.

HOW SUPPLIED

Aldactazide tablets containing 25 mg of spironolactone (Aldactone) and 25 mg of hydrochlorothiazide are round, tan, film coated, with SEARLE and 1011 debossed on one side and ALDACTAZIDE and 25 on the other side, supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
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<tbody>
<tr>
<td>0025-1011-31</td>
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Aldactazide tablets containing 50 mg of spironolactone (Aldactone) and 50 mg of hydrochlorothiazide are oblong, tan, scored, film coated, with SEARLE and 1021 debossed on the scored side and ALDACTAZIDE and 50 on the other side, supplied as:

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