

PRODUCT MONOGRAPH

ALDACTAZIDE* 25

(spironolactone and hydrochlorothiazide tablets USP)

tablets 25mg: 25mg

ALDACTAZIDE* 50

(spironolactone and hydrochlorothiazide tablets USP)

tablets 50mg: 50mg

Aldosterone Antagonist with a Diuretic

Pfizer Canada Inc.
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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ALDACTAZIDE*

(spironolactone and hydrochlorothiazide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablet : <ul style="list-style-type: none">▪ 25 mg spironolactone and 25 mg of hydrochlorothiazide or▪ 50 mg of spironolactone and 50 mg of hydrochlorothiazide.	Calcium sulfate, corn starch, magnesium stearate, peppermint flavouring, povidone, hypromellose, polyethylene glycol 400, carnauba wax, stearic acid, opaspray K-1-7076

INDICATIONS AND CLINICAL USE

Fixed-dose combination drugs are not indicated for initial therapy. Patients should be titrated on the individual drugs. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. If during maintenance therapy dosage adjustment is necessary, it is advisable to use the individual drugs.

ALDACTAZIDE (spironolactone and hydrochlorothiazide) is indicated for:

1. 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. The treatment of diuretic-induced hypokalemia in patients with congestive heart failure when other measures are considered inappropriate. The treatment of patients with congestive heart failure taking digitalis when other therapies are considered inadequate or inappropriate.

Cirrhosis of the liver accompanied by edema and/or ascites: Aldosterone levels may be exceptionally high in this condition. ALDACTAZIDE is indicated for maintenance therapy together with bed rest and the restriction of fluid and sodium.

The nephrotic syndrome: ALDACTAZIDE may be used in nephrotic patients who are not responsive to glucocorticoid therapy and who do not respond to other diuretics. However, ALDACTAZIDE has not been shown to affect the basic pathological process.

2. Essential hypertension

In patients with essential hypertension in whom other measures are considered inadequate or inappropriate. In hypertensive patients for the treatment of a diuretic induced hypokalemia when other measures are considered inappropriate.

CONTRAINDICATIONS

- Anuria
- Acute renal insufficiency
- Addison's disease
- Significant impairment of renal function
- Hyperkalemia
- Significant hypercalcemia
- Patients who are hypersensitive to spironolactone, thiazides or other sulfonamide-derived drugs, or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging Section.
- Concomitant use of eplerenone (see **Warnings and Precautions- Hyperkalemia, Drug Interactions sections**)
- Concomitant use of heparin, low molecular weight heparin (see **Warnings and Precautions- Hyperkalemia, Drug Interactions sections**)

ALDACTAZIDE (spironolactone and hydrochlorothiazide) may be contraindicated in patients with severe or progressive liver disease.

WARNINGS AND PRECAUTIONS

Avoid potassium supplements and foods (e.g., bananas, prunes, raisins, and orange juice) containing high levels of potassium including salt substitutes.

Follow your doctor's directions for a low-salt or low-sodium diet and daily exercise program.

General

Use only for "Indications": Use ALDACTAZIDE (spironolactone and hydrochlorothiazide) only for conditions described under "INDICATIONS".

Potassium (K⁺) Supplementation: The concurrent administration of potassium supplements, a diet rich in potassium, or other K⁺-sparing diuretics is not recommended as this may induce hyperkalemia.

Somnolence and dizziness: Somnolence and dizziness have been reported to occur in some patients sometimes leading to falls and fractures. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

Carcinogenesis and Mutagenesis

Tumorigenicity: Spironolactone, in chronic toxicity studies, has been shown to be a tumorigen in rats. Breast cancer and other neoplasms (intestinal, pancreas, etc) have been reported in postmarket surveillance.

Endocrine and Metabolism

Gynecomastia: Gynecomastia may develop with the use of spironolactone and physicians should be advised of its possible occurrence. The development of gynecomastia appears to be related to both dosage and duration of therapy and is normally reversible when the drug is discontinued. If gynecomastia develops, discontinue the drug. In rare instances some breast enlargement may persist.

Hyperchloremic metabolic acidosis: Reversible hyperchloremic metabolic acidosis, 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. Caution should be used in treating patients with acute or severe liver impairments, since vigorous diuretic therapy may precipitate hepatic encephalopathy.

Acidosis and Renal Function: Rare reports of acidosis have been reported with ALDACTAZIDE.

Hypochloremic alkalosis: Hypochloremic alkalosis occurs infrequently and is rarely severe. Unduly restricted dietary sodium may complicate therapy. A chloride deficit may be corrected by using ammonium chloride (except in renal or hepatic disease) and is largely prevented by a near-normal sodium/chloride intake.

Hematologic

Electrolyte Balance: Because of the diuretic action of ALDACTAZIDE, patients should be carefully evaluated for possible disturbance of fluid and electrolyte balance, due to the possibility of hyperkalemia, hypochloremic alkalosis, hyponatremia and possible BUN elevation, especially the elderly and/or patients with pre-existing impaired renal or hepatic function.

a) Hyperkalemia

Hyperkalemia may occur in patients treated with ALDACTAZIDE if the potassium intake is excessive. This can cause cardiac irregularities, some of which may be fatal. Hyperkalemia may occur in the absence of excessive potassium intake, particularly in patients with impaired renal function, elderly patients, or patients with diabetes. Consequently, no potassium supplementation should ordinarily be given with ALDACTAZIDE. ALDACTAZIDE should not be administered concurrently with other potassium-sparing diuretics. ALDACTAZIDE, when used with ACE inhibitors, Angiotensin II antagonists, other aldosterone blockers or indomethacin, even in the presence of a diuretic, has been associated with severe hyperkalemia (see **DRUG INTERACTIONS**).

Concomitant use of spironolactone with heparin, low molecular weight heparin may lead to severe hyperkalemia (See **Contraindications, Drug Interactions** section)

Hyperkalemia in Patients with Severe Heart Failure

As hyperkalemia may be fatal, it is critical to monitor and manage serum potassium in patients with severe heart failure receiving ALDACTAZIDE. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium > 3.5 mEq/L. No information is available regarding patients with serum creatinine > 2.5 mg/dL or a recent increase in serum creatinine >25%. The recommended monitoring for potassium and creatinine is one 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.

Hyperkalemia can be treated promptly by rapid intravenous administration of glucose (20 to 50%) and regular insulin, using 0.25 to 0.5 units of insulin per gram of glucose. This is a temporary measure to be repeated if required. ALDACTAZIDE should be discontinued and potassium intake (including dietary potassium) restricted.

b) Hypokalemia

Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis or during concomitant use of loop diuretics, glucocorticoids, or ACTH. Digitalis therapy may exaggerate the metabolic effects of hypokalemia especially with reference to myocardial activity. If hypokalemia occurs, ALDACTAZIDE should be discontinued and consideration given to one of the following therapeutic regimens:

1. use of hydrochlorothiazide alone with potassium supplementation as needed, or
2. use of spironolactone (ALDACTONE) alone.

c) Hyponatremia

During the administration of ALDACTAZIDE patients suffering from sodium depletion must be attentively monitored and signs of electrolyte imbalance must be carefully checked.

ALDACTAZIDE may, if administered concomitantly with other diuretics, cause or aggravate hyponatremia, as manifested by dryness of the mouth, thirst, lethargy, and drowsiness.

A true low-salt syndrome may develop with ALDACTAZIDE therapy and may be manifested by increasing mental confusion similar to that observed with hepatic coma. This syndrome was differentiated from dilutional hyponatremia in that it does not occur with obvious fluid retention. Its treatment requires that diuretic therapy be discontinued and sodium administered.

Hepatic/Biliary/Pancreatic

Impaired Hepatic Function: ALDACTAZIDE should be used with caution in patients with impaired hepatic function, because minor alterations in electrolyte balance may precipitate hepatic coma. In the treatment of the edema/ascites of cirrhosis, when high doses of ALDACTAZIDE are required, it is recommended that the drug dosage be decreased before diuresis is complete, in order to avoid dehydration. If mental confusion occurs, ALDACTAZIDE should be temporarily discontinued.

Neurologic: Lithium generally should not be given with diuretics. Thiazide diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Acute renal failure, sometimes fatal, has been observed. Lithium dose adjustment may be required (see **DRUG INTERACTIONS**).

Renal: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Sexual Function/Reproduction: In a reproduction study in which female rats received dietary doses of 15 and 50 mg/kg/day spironolactone, there were no effects on mating or fertility, but there was a small increase in incidence of stillborn pups at the higher dose. When injected into female rats (100 mg/kg/day, 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 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 i.p.) administered to female mice, decreased the number of mated mice that conceived and decreased the number of implanted embryos in those that became pregnant; at 200 mg/kg/day it also increased the latency period to mating.

Miscellaneous

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates or narcotics.

Pathological changes in the parathyroid gland, with resultant hypercalcemia and hypophosphatemia, have been observed in a few patients on prolonged thiazide therapy.

Exacerbation or activation of systemic lupus erythematosus has been reported for sulfonamide derivatives, including thiazides (see ADVERSE REACTIONS section).

Thiazides may increase the concentration of blood uric acid. Caution is necessary in patients with hyperuricemia or a history of gout, because gout may be precipitated by thiazides. Dosage adjustment of anti-gout medications may be necessary.

In diabetic and prediabetic patients, thiazides may increase blood glucose concentrations. Dosage adjustments of insulin or hypoglycemic medications may be required.

Special Populations

Pregnant Women: Spironolactone and its metabolites may, and thiazides do cross the placental barrier and appear in cord blood. Thiazides may decrease placental perfusion, increase uterine inertia, and inhibit labour. There are no studies in pregnant women. When ALDACTAZIDE is used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In rats, feminization of the male fetus has been reported at high doses.

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, dose-related hypoprolactinemia and decreased ventral prostate and seminal vesicle weights in males, and increased leutinizing hormone secretion and ovarian and uterine weights in females were reported. Feminization of the external genitalia of male fetuses was reported in another rat study.

Nursing Women: Certain adverse reactions to thiazide therapy (e.g. hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism) can occur in the newborn since thiazides have been demonstrated to appear in breast milk. Canrenone, a major (and active) metabolite of spironolactone, and thiazides appear in human breast milk. Because of the unknown potential for adverse events on the breastfeeding infant, a decision should be made whether to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.

Monitoring and Laboratory Tests

General: ALDACTAZIDE therapy may result in a transient elevation of BUN, especially when azotemia exists at the beginning of treatment. This appears to represent a concentration phenomenon rather than renal toxicity, since the BUN returns to normal after ALDACTAZIDE is discontinued. Progressive elevation of BUN is suggestive of the presence of pre-existing renal impairment.

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 this interference (which may be assay-specific) has been fully established.

Discontinue spironolactone for at least 4, and preferably 7, days prior to plasma cortisol determinations, if they are to be done by the method of Mattingly, that is, by fluorometric assay. No interference has been demonstrated with the competitive protein binding technique or radioimmunoassay technique.

Thiazides may decrease serum PBI levels without evidence of alteration of thyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide therapy.

Adrenal Vein Catheterization and Plasma Renin Activity: Discontinue spironolactone several days prior to adrenal vein catheterization for measurement of aldosterone concentrations and measurements of plasma renin activity.

ADVERSE REACTIONS

The adverse reactions encountered most frequently are gynecomastia and gastrointestinal symptoms. Adverse reactions due to ALDACTAZIDE (spironolactone and hydrochlorothiazide) are usually reversible upon discontinuation of ALDACTAZIDE. In rare instances, some gynecomastia may persist.

A. Spironolactone

The adverse reactions encountered most frequently with spironolactone are gynecomastia and gastrointestinal symptoms. The following adverse reactions have been reported in association with spironolactone:

Body as a Whole: Malaise

Digestive: Diarrhea and cramping, gastric bleeding, gastritis, nausea, ulceration, vomiting.

Hematologic: Leukopenia (including granulocytosis), thrombocytopenia, **anemia**.

Hypersensitivity: Drug fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis, pruritus, rash.

Liver/biliary: mixed cholestatic/hepatocellular toxicity (some fatal).

Metabolism: Electrolyte disturbances (hypochloremic alkalosis, hyponatremia, hypokalemia, hyperkalemia), see WARNINGS and PRECAUTIONS-Electrolyte Balance.

Musculoskeletal: Leg cramps, rhabdomyolysis, myalgia, weakness

Nervous system/psychiatric: Mental confusion, ataxia, headache, drowsiness, dizziness, lethargy, change in libido.

Renal: Renal dysfunction (including acute renal failure)

Reproduction: gynecomastia (see WARNINGS and PRECAUTIONS- Carcinogenesis and Mutagenesis), impotence, inability to achieve or maintain erection, abnormal semen (decreased motility and sperm count), irregular menses or amenorrhea, postmenopausal bleeding, benign breast neoplasm, breast pain, breast carcinoma (including in male patients).

Respiratory: Dysphonia, dyspnea

Skin and appendages: alopecia, hypertrichosis.

B. Hydrochlorothiazide

Cardiovascular: Orthostatic hypotension (may be potentiated by alcohol, barbiturates or narcotics).

Central Nervous System: dizziness, vertigo, paresthesia, headache, xanthopsia.

Gastrointestinal: anorexia, gastric irritation, nausea, vomiting, cramps, diarrhea, constipation, jaundice (intrahepatic cholestatic), acute pancreatitis, sialoadenitis.

Hematologic: Leukopenia, thrombocytopenic purpura, agranulocytosis, aplastic anemia, hemolytic anemia.

Hypersensitivity: purpura (including thrombocytopenic), photosensitivity, rash, urticaria, necrotizing angitis, pruritus and erythema multiforme, respiratory distress including pneumonitis and pulmonary edema, fever, anaphylactic reactions.

Miscellaneous: Muscle spasm, weakness, restlessness, nitrogen retention, hypokalemia, hyperglycemia, glycosuria, hypomagnesemia, hyponatremia, hyperuricemia, transient blurred vision, alopecia.

Adverse reactions due to ALDACTAZIDE (spironolactone and hydrochlorothiazide) are usually reversible upon discontinuation of ALDACTAZIDE. In rare instances, some gynecomastia may persist.

POST-MARKET ADVERSE EVENTS

Table 1 Based on post-marketing spontaneous adverse event reports. The percentages shown are calculated as the number of adverse events reported per 100 patient years exposure to spironolactone/hydrochlorothiazide. The causal relationship between spironolactone/hydrochlorothiazide and the emergence of these events has not been clearly established.

Adverse Event	Estimated Reporting Rate			
	Reported Commonly ≥ 1%	Reported Uncommonly < 1% and ≥ 0.1%	Reported Rarely < 0.1% and ≥ 0.01%	Reported Very Rarely < 0.01%
Blood and lymphatic system disorders				
Thrombocytopenia				X
Agranulocytosis				X
Anaemia				X
Leukopenia				X
Cardiac disorders				
Bradycardia (n=2)				X
Myocardial infarction*				X
Tachycardia (n=1)				X
Arrhythmia*				X
Atrioventricular block*				X
Atrial fibrillation*				X
Bundle branch block, Bundle branch block right*				X
Cardiac failure (+/-congestive) (n=1)				X
Right Ventricular failure*				X
Torsade de pointes*				X
Ear and labyrinth disorders				
Vertigo				X
Endocrine disorders				
Inappropriate ADH secretion (n=2)				X
ADH abnormality*				X
Hyperthyroidism*				X
Gastrointestinal disorders				
Vomiting				X
Nausea				X
Diarrhoea				X
Pancreatitis acute (necrotizing, relapsing)				X
Abdominal pain				X
Gastrointestinal haemorrhage (rectal haemorrhage)				X
Constipation				X
Melaena				X
General disorders and administration site conditions				
Malaise				X
Asthenia				X
Pyrexia				X

Adverse Event	Estimated Reporting Rate			
	Reported Commonly ≥ 1%	Reported Uncommonly < 1% and ≥ 0.1%	Reported Rarely < 0.1% and ≥ 0.01%	Reported Very Rarely < 0.01%
Chest pain				X
Oedema (peripheral + other)				X
Sudden death (n=1)*				X
Hepatobiliary disorders				
Jaundice				X
Cholestasis				X
Hepatitis*				X
Hepatomegaly*				X
Hepatic steatosis / necrosis / failure (reported 1 time each)				X
Infections and infestations				
Pneumonia*				X
Otitis media				X
Investigations				
Weight decreased*				X
Blood creatinine increased*				X
Gamma-glutamyltransferase increased*				X
Aspartate aminotransferase increased*				X
Alanine aminotransferase increased*				X
Transaminases increased*				X
Increased weight due to increased peripheral edema* (after switching to generic)				X
Immune system disorders				
Hypersensitivity				X
Metabolism and nutrition disorders				
Hyponatraemia				X
Hypomagnesaemia				X
Hyperkalaemia				X
Hypochloraemia				X
Hypercalcaemia				X
Dehydration				X
Decreased appetite				X
Metabolic acidosis				X
Increased abdominal fat tissue (after 1 year of treatment)*				X
Hypoglycaemia*				X
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis*				X
Myalgia, Muscular weakness				X
Systemic lupus erythematosus				
Neoplasms benign, malignant and unspecified (including cysts & polyps)				

Adverse Event	Estimated Reporting Rate			
	Reported Commonly ≥ 1%	Reported Uncommonly < 1% and ≥ 0.1%	Reported Rarely < 0.1% and ≥ 0.01%	Reported Very Rarely < 0.01%
Breast cancer (female, male) Neoplasm malignant (n=2): - Uterine leiomyoma* - Adenocarcinoma pancreas (n=1) - Hepatic cancer metastatic (n=1) - Lung neoplasm malignant* - Lymphoma				X X X X X X
Nervous system disorders Somnolence Dizziness / Balance disorder Coma (Including Hepatic) (n=1) Loss (n=1)/ Altered*/ Depressed* consciousness Syncope* Convulsions (n=1) Cerebrovascular accident / disorder* Brain oedema* Paraesthesia				X X X X X X X X X
Psychiatric disorders Confusional state Disorientation Depression(n=1) Aggression* Agitation* Abnormal behaviour* Suicide attempt (n=1)*				X X X X X X X
Renal and urinary disorders Renal failure (acute, chronic) Renal impairment Tubulointerstitial nephritis* Oliguria (n=1) Anuria*				X X X X X
Respiratory, thoracic and mediastinal disorders Dyspnoea Pulmonary fibrosis (n=1) Respiratory failure* Pulmonary embolism (n=1) Pulmonary oedema* Interstitial lung disease* Cough*				X X X X X X X
Skin and subcutaneous tissue disorders Purpura Pruritus Rash maculo-papular, erythematous Photosensitivity reaction				X X X X

Table 1. Post-market Serious Spontaneous Adverse Event Reports

<i>Adverse Event</i>	<i>Estimated Reporting Rate</i>			
	<i>Reported Commonly ≥ 1%</i>	<i>Reported Uncommonly < 1% and ≥ 0.1%</i>	<i>Reported Rarely < 0.1% and ≥ 0.01%</i>	<i>Reported Very Rarely < 0.01%</i>
Dermatitis bullous*				X
Eczema*				X
Toxic epidermal necrolysis / eruption*				X
Pemphigoid*				X
Vascular disorders				
Orthostatic hypotension				X
Hypotension				X
Circulatory collapse*				X
Arteriosclerosis (n=1)				X
Shock haemorrhagic (n = 1)*				X
Haemorrhage (n = 1)				X

Source: IMS exposure data from 2nd quarter 1998 to 1st quarter 2010; spironolactone / thiazides cumulative report (Reporting Period: 10 November 1960 to 09 November 2009).

* The events indicated (*) have not been reported for Aldactazide, however, they have been reported for other spironolactone/thiazide combination products (spironolactone/butizide and spironolactone/hydroflumethiazide).
n= number

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2. Established or Potential Drug-Drug Interactions

Drug Interaction	Effect	Clinical comment
Alcohol, barbiturates or narcotics	Potential of orthostatic hypotension may occur.	
Antipyrine	Spironolactone enhances the metabolism of antipyrine.	
Cholestyramine/ Colestipol and Ammonium Chloride	Cholestyramine and colestipol reduce the absorption of thiazides and may reduce their diuretic effects. Hyperchloremic metabolic acidosis, frequently associated with hyperkalemic, has been reported in patients given spironolactone concurrently with ammonium chloride or cholestyramine.	
Corticosteroids, ACTH	Intensified electrolyte depletion, particularly hypokalemia, may occur	
Diuretics and Antihypertensives	Although ALDACTAZIDE (spironolactone and hydrochlorothiazide) may be administered concomitantly with diuretics and antihypertensives, the effect is additive. In these cases, orthostatic hypotension, malaise, loss consciousness, vomiting, falls and femur fracture were observed. Hyperkalemia has been associated with the use of angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists and aldosterone blockers in combination with spironolactone.	It is advisable to reduce the dose of these drugs. In particular, the dose of ganglionic blocking agents should be reduced by at least 50% when ALDACTAZIDE is included in the regimen.
Eplerenone	Severe hyperkalemia has been associated with the use of aldosterone blockers in combination with spironolactone.	
Heparin, low molecular weight heparin	Concomitant use of spironolactone with heparin, low molecular weight heparin may lead to severe hyperkalemia.	

Drug Interaction	Effect	Clinical comment
Insulin and Hypoglycemics Antidiabetic drugs (e.g. oral agents)	Insulin requirements and dosage of hypoglycemic medication in diabetics may be increased, decreased or unchanged. Erythema multiforme was observed when ALDACTAZIDE and glibenclamide were coadministered. Hyperglycemia may occur with thiazide diuretics	Hyperglycemia and glycosuria may be manifested in latent diabetics. Dosage adjustment of the hypoglycemic drug may be required
Lithium*	Thiazide diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. Cotreatment with ALDACTAZIDE was associated with acute renal failure, sometimes fatal.	Lithium dose adjustment may be required.
Norepinephrine	Hydrochlorothiazide and spironolactone each reduce vascular responsiveness to norepinephrine.	Caution should be exercised in the management of patients subjected to regional or general anaesthesia while being treated with ALDACTAZIDE. Consideration should be given to discontinuation of ALDACTAZIDE therapy prior to elective surgery.
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 dose of digoxin when spironolactone is administered, and the patient should be carefully monitored to avoid over- or under-digitalization. Two mechanisms of possible interaction: a) Spironolactone and its metabolites interfere with digoxin radioimmunoassay or b) alter the pharmacokinetics of digoxin. The occurrence of either or both of these processes may make interpretation of serum digoxin levels difficult.
Non-Steroidal Anti-Inflammatory Drugs	It has been reported that ASA, mefenamic acid, and indomethacin have been shown to attenuate the diuretic action of spironolactone, possibly due to inhibition of intrarenal synthesis of prostaglandins. Hyperkalemia has been associated with the use of indomethacin in combination with potassium-sparing diuretics.	However, it has been shown that ASA does not alter the effect of spironolactone on blood pressure, serum electrolytes, urea nitrogen, or plasma renin activity in hypertensive patients.
Skeletal muscle relaxants, non-depolarizing (e.g. tubocurarine)	Thiazides may increase responsiveness to skeletal muscle relaxants.	

Drug Interaction	Effect	Clinical comment
Atorvastatin* + furosemide + ASA	Hepatitis, pancreatitis, death have been reported with cotreatment with ALDACTAZIDE.	

* Occurrence of death

Drug-Food Interactions

Food increased both rate (C_{max}) and extent (AUC) of exposure to spironolactone and its active metabolite, canrenone, following a 200 mg dose of spironolactone (given as two 100 mg Aldactone tablets). In a 9 subject study, statistically significant increases of approximately 2-fold in spironolactone $AUC_{(0-24)}$ and greater than 2-fold in C_{max} were reported after food co-administration. At the same time, increases of approximately 1.4-fold were seen in C_{max} and $AUC_{(0-24)}$ of canrenone. The clinical importance of increased exposure due to co-administration with food has not been studied. However, if ALDACTAZIDE is administered with food, patients should be monitored for signs that can be associated with excessive exposure such as increased serum potassium levels and other serious symptoms (see Overdosage section), particularly in patients with impaired renal and hepatic function, pregnant/nursing women and elderly patients, particularly in patients with impaired renal function.

Drug-Laboratory Test Interactions

Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides may also decrease serum protein-bound iodine (PBI) levels without evidence of alteration of thyroid function. It was shown that hydrochlorothiazide is effective in increasing 24h ^{131}I uptake rate and augmenting ^{131}I absorbed dose of thyroid remnant.

Several reports of possible interference with digoxin radioimmunoassay assays by spironolactone, or its metabolites, have appeared in the literature. Increase of spironolactone concentrations by 2-4 fold 2-24h post-dose after coadministration with digoxin in healthy volunteers. Also, increase of digoxin levels when given with spironolactone. Hence, dose adjustment for both ALDACTAZIDE and digoxin is necessary and safety monitoring required.

DOSAGE AND ADMINISTRATION

Food effect on Aldactazide pharmacokinetics has been observed (see Food-Drug Interaction section). Dose adjustment may be considered.

Optimal dosage should be established by individual titration of the components.

Treatment should be continued for 2 weeks before optimal effectiveness can be assessed.

Edema in adults: (congestive heart failure, hepatic cirrhosis or nephrotic syndrome): Daily dosage of 2 to 4 tablets of ALDACTAZIDE 25 or 1 to 2 tablets of ALDACTAZIDE 50 in single or divided doses should be adequate for most patients, but may range from 2 to 8 tablets daily of ALDACTAZIDE 25 or 1 to 4 tablets of ALDACTAZIDE 50.

Edema in children: The usual daily maintenance dose of ALDACTAZIDE should be that which provides 0.75 to 1.5 mg of spironolactone per pound of body weight (1.65 to 3.3 mg/kg).

Essential hypertension: In essential hypertension, a daily dosage of 2 to 4 ALDACTAZIDE 25 tablets or 1 to 2 ALDACTAZIDE 50 tablets in single or divided doses, will be adequate for most patients, but may range from 2 to 8 tablets of ALDACTAZIDE 25 or 1 to 4 tablets of ALDACTAZIDE 50.

Since ALDACTAZIDE increases the action of other antihypertensive drugs, especially the ganglionic blocking agents, the dosage of such drugs should be reduced by at least 50% when ALDACTAZIDE is added to the regimen.

OVERDOSAGE

Symptoms: There have been no reports of fatal overdose in man (except indirectly through hyperkalemia). Nausea and vomiting occurs, and (much more rarely) drowsiness, dizziness, decreased consciousness, coma, mental confusion, diarrhea, or a maculopapular or erythematous rash. These manifestations disappear promptly on discontinuation of medication. Hyperkalemia may be exacerbated. Thrombocytopenic purpura and granulocytopenia have occurred with thiazide therapy.

Treatment: No specific antidote. No persistent toxicity has occurred or is expected. Spironolactone/hydrochlorothiazide use should be discontinued and potassium intake (including dietary sources) restricted.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action: ALDACTAZIDE (spironolactone and hydrochlorothiazide) is a combination of two diuretic agents with different but complementary mechanisms and sites of action. The spironolactone component helps to minimize the potassium loss, which may be induced by the thiazide component. Spironolactone is a specific pharmacologic antagonist of the adrenal mineralocorticoid, aldosterone, acting primarily through competitive binding with receptors at the aldosterone-dependent sodium/potassium exchange site in the distal convoluted renal tubule. Hydrochlorothiazide promotes excretion of sodium and water primarily by

inhibiting their reabsorption by the cortical diluting segment of the renal tubule, in contrast to spironolactone, which exerts its effect more distally. Both spironolactone and hydrochlorothiazide reduce exchangeable sodium and plasma volume.

Pharmacokinetics: The effects of hydrochlorothiazide will be observed on the day of administration, but the spironolactone component does not attain its maximal effect until the third day.

Spironolactone is rapidly and extensively metabolized to a number of metabolites including canrenone and the sulfur-containing 7-thiomethylspironolactone, both of which are pharmacologically active. Approximately 25 to 30% of the dose administered is converted to canrenone, which attains peak serum levels 2-4 hours after single oral administration of spironolactone. In the dose range of 25 mg to 200 mg, an approximately linear relationship exists between a single dose of spironolactone and plasma levels of canrenone.

Plasma concentrations of canrenone decline in two distinct phases, the first phase lasting from 3 to 12 hours, being more rapid than the second phase lasting from 12 to 96 hours. Canrenone clearance data, following multiple doses of spironolactone, indicate that accumulation of canrenone in the body with 100 mg once a day would be lower than with 25 mg four times a day. Both spironolactone and canrenone are more than 90-percent bound to plasma proteins. The metabolites of spironolactone are excreted both in the urine (32-53%), and through biliary excretion in the feces (14-36%).

Table 3. Summary of Pharmacokinetic Parameters of Spironolactone (ALDACTONE) in Healthy Volunteers Administered 100 mg daily for 15 days

	Mean C _{max} (ng/mL)	Mean T _{max} (h)	Mean Post-Steady State t _{1/2} (h)	Accumulation Factor: AUC _{0-24 h, Day 15} / AUC _{0-24 h, Day 1}
7- α -(thiomethyl) spironolactone (TMS)	391	3.2	13.8	1.25
6- β -hydroxy-7- α - (thiomethyl) spironolactone (HTMS)	125	5.1	15.0	1.50
Canrenone (C)	181	4.3	16.5	1.41
Spironolactone	80	2.6	~1.4 (t _{1/2} β)	1.30

Hydrochlorothiazide is rapidly absorbed following oral administration, with onset of action occurring within one hour, and the duration of action is 6 to 12 hours. Plasma concentration attains a peak at 1 to 2 hours and declines with a half-life of 4 to 5 hours. Hydrochlorothiazide undergoes only slight metabolic alteration and is excreted in the urine. It is distributed throughout the extracellular space, with essentially no tissue accumulation except in the kidney. Hydrochlorothiazide is eliminated rapidly by the kidney.

STORAGE AND STABILITY

Store at 15 to 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ALDACTAZIDE 25:

Each light tan round, biconvex, film-coated tablet, debossed "ALDACTAZIDE" and "25" on one side, and "SEARLE" and "1011" on the other. Peppermint odor. Contains spironolactone 25 mg and hydrochlorothiazide 25 mg.

Non-medicinal ingredients include: Calcium sulfate, corn starch, magnesium stearate, peppermint flavouring, povidone, hypromellose, polyethylene glycol 400, carnauba wax, stearic acid, opaspray K-1-7076.

Available in bottles of 100 tablets.

ALDACTAZIDE 50:

Each light tan capsule-shaped, scored, film-coated tablet debossed "ALDACTAZIDE" and "50" on one side, and "SEARLE", "1021" on the other. Peppermint odor. Contains spironolactone 50 mg and hydrochlorothiazide 50 mg.

Non-medicinal ingredients: Calcium sulfate, corn starch, magnesium stearate, peppermint flavouring, povidone, hypromellose, polyethylene glycol 400, carnauba wax, stearic acid, opaspray K-1-7076.

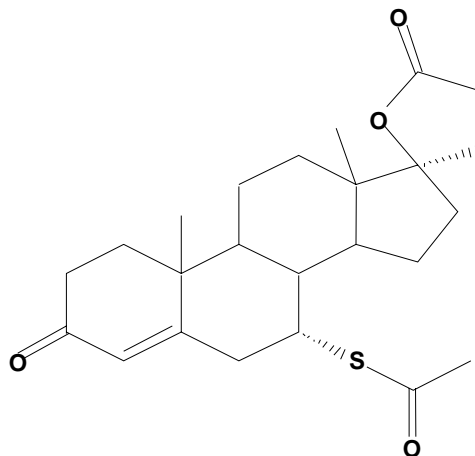
Available in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

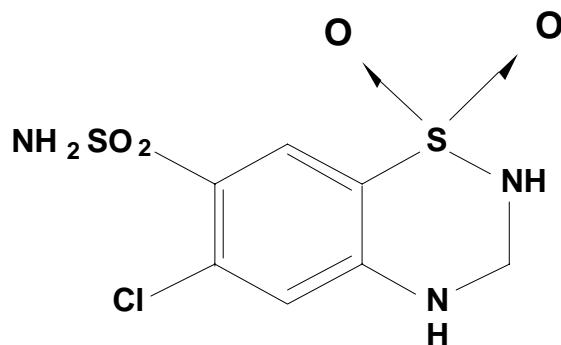
Drug Substance

- A. Proper name: Spironolactone
- Chemical name: 17-hydroxy-7 α -mercapto-3-oxo-17 α -pregn-4-ene-21-carboxylic acid- γ - lactone acetate
- Molecular formula: C₂₄H₃₂O₄S
- Molecular mass: 416.59
- Structural formula:



- Description: Spironolactone is a synthetic, yellowish, crystalline solid and belongs to the steroid class of chemical compounds. Spironolactone is insoluble in water, but soluble in most organic solvents.

- B. Proper name: Hydrochlorothiazide
- Chemical name: 6-chloro-3,4-dihydro-7-sufamoyl-2H-1,2,4-benzothiadiazene 1,1-dioxide
- Molecular formula: $C_7H_8ClN_3O_4S_2$
- Molecular mass: 297.75
- Structural formula:



Description: Hydrochlorothiazide is a white, crystalline, odorless powder, with a slightly bitter taste. It is practically insoluble in water, but is soluble in dilute ammonia or sodium hydroxide. It is also soluble in methanol, ethanol, and acetone, but is insoluble in chloroform and ether.

TOXICOLOGY

A. Spironolactone

Acute toxicity of spironolactone

Species	Route	LD ₅₀ ± Standard Error (mg/kg)
Mouse	Intragastric	>1000
	Intraperitoneal	356 ± 94
Rat	Intragastric	>1000
	Intraperitoneal	786 ± 125
Rabbit	Intragastric	>1000
	Intraperitoneal	866 ± 156

Long-Term Toxicity

Species / Number	Length of study	Dose (mg/kg/d)	Results
Spironolactone			
Rat (25/sex/gp)	26 w	0, 120, 300, 700	Only minor changes: dose-related increase in liver weights
Rat (36/sex/gp)	78 w	0, 50, 150, 500	Significant dose-related increase in benign adenomas of thyroid follicular cells and testicular interstitial cells. In male rats, there was a dose-related increase in proliferative changes in the liver including hyperplastic nodules and hepatocellular carcinomas.
Rat (30/sex/gp)	104 w	0, 10, 30, 100	Significant dose-related increase in benign adenomas of thyroid follicular cells. Dose-related increase in liver weights.
Dog (2/sex/gp)	13 w	0, 12, 30, 70 (1-6 w); 100 (7-9 w); 250 (10-13 w)	No treatment-related findings.
Monkey (12/sex/gp)	26 w	0, 125	No treatment-related changes or tumors
Monkey (4/sex/gp)	52 w	0, 20, 50, 125 (1-9 w); 0, 20, 50, 250	No tumors. Increased liver weights in males at high dose after 1 year. Dose-related increase of acinar tissue of mammary gland in males.
Potassium Canrenoate			
Rat (20M, 25F/gp)	26 w	0, 10, 60, 360	High dose: increased serum levels of albumin and protein in females. Increase in SGPT in males and females. Hypertrophy of thyroid and adrenal glands. Increase in hypertrophy of FSH cells. Mammary

Species / Number	Length of study	Dose (mg/kg/d)	Results
			tumors (4 females), adenoma (1 rat), fibro-adenoma (1 rat), adenocarcinoma (1 rat, 60 mg/kg).
Rat (28/sex/gp) (8/sex/gp sacrificed at 13 w)	52 w	0, 30, 90, 270	Granulocytic leukemia in peripheral blood and bone marrow in males and females. Mammary tumors in 14 female rats (3 mid-doses, 8 high-dose).
Rat (50/sex/gp)	104 w	0, 20, 50, 125, 270	Granulocytic leukemia and hepatic, thyroid, testicular and mammary tumors.
Dog (4/sex/gp)	26 w	0, 10, 45, 200	Hypertrophy of mammary glands with secretion of milky substance, increased uterine weight. Proliferation of pituitary cells producing prolactin, hyperplasia of the endometrium, atrophy of the prostate gland and hyperplasia of zona glomerulosa of the adrenal gland.

Seminal vesicles and prostate in rats, dogs and monkeys were significantly reduced in weight. There was a dose-related maturation arrest of the testes in rats treated for 78 and 104 weeks and monkeys treated for 52 weeks.

Mutagenicity

Potassium canrenoate did not produce a mutagenic effect in tests using bacteria and yeast. It did produce a positive mutagenic effect in several *in vitro* tests in mammalian cells usually requiring metabolic activation. In an *in vivo* mammalian system, potassium canrenoate was not mutagenic at doses up to 270 mg/kg.

There was no increased incidence of leukemia in rats treated with spironolactone for up to 104 weeks at doses up to 500 mg/kg/day.

Teratogenicity

Teratogenicity studies have been conducted in mice, rats and rabbits administered oral doses of spironolactone (0-50 mg/kg).

In these studies, spironolactone had no embryonic effects in mice or rats. Limited dose-related teratogenic effects (hypoprolactinemia and decreased ventral prostate and seminal vesicle weights in males; increased leutinizing hormone secretion and ovarian and uterine weights in females) were reported in one rat study at doses of 50 and 100 mg/kg/day. Feminization of the external genitalia of male fetuses was reported in another study in rats at 200 mg/kg/day doses. Rabbits receiving 20 mg/kg/day (highest dose administered) had a decreased conception rate, an increased rate of resorption and a lower number of live pups.

B. Hydrochlorothiazide

Hydrochlorothiazide has been shown to be hepatotoxic (fatty degeneration, glycogen depletion, periportal inflammation) in rats. A significant reduction in serum potassium occurred. These hepatotoxic effects are not influenced by oral administration of potassium.

Dogs (N=40; 13-23 kg) administered oral hydrochlorothiazide (up to 200 mg/day) for up to 9 months, developed the following toxicity:

- significant hypercalcemia
- hypophosphatemia.
- Enlarged and hyperactive parathyroid glands.

C. Spironolactone And Hydrochlorothiazide

Long-Term Toxicity

	Length of study	Dose (mg/kg/d)	Results
Spironolactone And Hydrochlorothiazide			
Rat	4 mo	Ratio of spironolactone: hydrochlorothiazide (3:1) 56.3, 147.6, 149.7	Growth slightly but significantly retarded (high-dose male, low-dose female). Increased lipid in zona glomerulosa of the adrenals – not dose-related (in females more than males). Foci of myocardial necrosis (mainly low-dose males; one high-dose male; not significant in females)
Dog	4 mo	Ratio of spironolactone: hydrochlorothiazide (3:1) 60, 160	Slight increase, within the normal range in plasma non-protein nitrogen. Reduced potassium and chloride levels, especially in females.

Teratogenicity

ALDACTAZIDE (spironolactone and hydrochlorothiazide) (0 and 20 mg/kg/day) was administered to albino rats from Day 5 to Day 15 of gestation. The only anatomic alterations in the test fetuses that differed significantly from controls were retarded closure of the skull and wavy appearing ribs in pups from two females. The incidence of retarded closure of the skull did not exceed that found in control groups in other studies. The significance of the wavy appearing ribs is unknown.

When ALDACTAZIDE (0 and 20 mg/kg/day) was administered to albino rabbits from Day 6 to Day 18 of gestation, no compound-related effects were noted.

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PART III: CONSUMER INFORMATION

ALDACTAZIDE

(spironolactone and hydrochlorothiazide)

This leaflet is part III of a three-part Product Monograph published when ALDACTAZIDE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ALDACTAZIDE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ALDACTAZIDE is used to treat high blood pressure and fluid retention (edema) caused by various conditions, including heart disease, cirrhosis of the liver and nephrotic syndrome.

What it does:

ALDACTAZIDE is a combination product. It contains spironolactone which belongs to the class of medicines known as aldosterone receptor antagonists.

ALDACTAZIDE also contains hydrochlorothiazide which belongs to the group of medicines known as diuretics, sometimes known as 'water pills'.

ALDACTAZIDE causes the kidney to eliminate unneeded water and sodium from the body into the urine, but also reduces the loss of potassium.

When it should not be used:

You should not use this medicine if you have had an allergic reaction to spironolactone, thiazides or other sulfonamide drugs, or if you have kidney disease, liver disease, high levels of potassium (hyperkalemia) or calcium (hypercalcemia) in your blood, or if you are pregnant or unable to urinate.

What the medicinal ingredient is:

Spironolactone and hydrochlorothiazide tablets.

What the nonmedicinal ingredients are:

Each ALDACTAZIDE 25 mg and 50 mg tablet contains calcium sulfate, corn starch, magnesium stearate, peppermint flavouring, povidone, hypromellose, polyethylene glycol 400, carnauba wax, stearic acid, opaspray K-1-7076.

What dosage forms it comes in:

Tablets: 25/25 mg and 50/50 mg of spironolactone and hydrochlorothiazide

WARNINGS AND PRECAUTIONS

Avoid potassium supplements and foods (e.g., bananas, prunes, raisins, and orange juice) containing high levels of potassium including salt substitutes.

Follow your doctor's directions for a low-salt or low-sodium diet and daily exercise program

Before you receive ALDACTAZIDE,

- tell your doctor and pharmacist if you are allergic to spironolactone, hydrochlorothiazide, any of the non-medicinal ingredients listed in the "What the nonmedicinal ingredients are" section earlier in this document, sulfa drugs, or any other drugs.
- tell your doctor and pharmacist what prescription, nonprescription medications and natural health products you are taking, especially low molecular weight heparins and/or heparin which is used to prevent blood clotting (coagulation); aspirin, lithium, medications for arthritis, diabetes, or high blood pressure, potassium supplements and vitamins.
- tell your doctor and pharmacist if you are taking eplerenone (INSPRA)
- tell your doctor if you have or have ever had diabetes, gout, or kidney or liver disease or skin problems (e.g. lupus).
- tell your doctor if you are pregnant, plan to become pregnant, or are breast-feeding. If you become pregnant while taking ALDACTAZIDE, call your doctor.
- if you are having surgery, including dental surgery, tell the doctor or dentist that you are taking ALDACTAZIDE.

Also,

- you should know that this drug may make you drowsy and dizzy (sometimes leading to falls and fractures or broken bones). Do not drive a car or operate machinery until you know how this drug affects you. Remember that alcohol can add to the drowsiness caused by this drug.
- Orthostatic hypotension (low blood pressure while you are standing) may occur and may be enhanced by alcohol, barbiturates or narcotics.
- Your doctor may need to monitor the electrolyte balance of your blood by a blood test.

INTERACTIONS WITH THIS MEDICATION

You should always tell your physician about all drugs you are taking including prescription, non-prescription and natural health products.

Drugs that may interact with ALDACTAZIDE include: aspirin, lithium, digoxin, antipyrine, cholestyramine, eplerenone, heparin, low molecular weight heparins, corticosteroids, norepinephrine, skeletal muscle relaxants, non-depolarizing (e.g.: tubocurarine), eplerenone (Inspra) atorvastatin along with furosemide and with aspirin as well as and medications for arthritis, diabetes, or high blood pressure.

PROPER USE OF THIS MEDICATION

Always follow your doctor's instructions carefully.

ALDACTAZIDE comes as a tablet to take by mouth. It is usually taken once a day in the morning.

Food increases the effect of ALDACTAZIDE. Patients with kidney and liver problems, pregnant or nursing women and the elderly are particularly at risk. If you take this medication with food, your doctor must monitor you for signs that can be associated with excessive exposure of ALDACTAZIDE. Overdose symptoms include nausea, vomiting, drowsiness, dizziness, decreased consciousness, coma, mental confusion, diarrhea, red spots/bruising/rash and irregular results on blood tests including increased serum potassium levels. These symptoms usually disappear when ALDACTAZIDE is discontinued. Take ALDACTAZIDE exactly as directed by your health care professional. Do not take more or less of it or take it more often than prescribed by your doctor.

This medication controls high blood pressure but does not cure it. Continue to take ALDACTAZIDE even if you feel well. Do not stop taking ALDACTAZIDE without talking to your doctor.

Usual dose

Edema in adults: (congestive heart failure, hepatic cirrhosis or nephrotic syndrome): Daily dosage of 2 to 4 tablets of ALDACTAZIDE 25 or 1 to 2 tablets of ALDACTAZIDE 50 in single or divided doses should be adequate for most patients, but may range from 2 to 8 tablets daily of ALDACTAZIDE 25 or 1 to 4 tablets of ALDACTAZIDE 50.

Edema in children: The usual daily maintenance dose of ALDACTAZIDE should be that which provides 0.75 to 1.5 mg of spironolactone per pound of body weight (1.65 to 3.3 mg/kg).

Essential hypertension: A daily dosage of 2 to 4 ALDACTAZIDE 25 tablets or 1 to 2 ALDACTAZIDE 50 tablets in single or divided doses, will be adequate for most patients, but may range from 2 to 8 tablets of ALDACTAZIDE 25 or 1 to 4 tablets of ALDACTAZIDE 50.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose: Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a missed one.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Although side effects from ALDACTAZIDE are not common, they can occur. Tell your doctor if any of these symptoms do not go away:

Gastrointestinal: Decreased appetite, gastric irritation, upset stomach, dryness of mouth, abdominal pain, nausea, vomiting, cramps, diarrhea, and constipation.

Central nervous system: Dizziness, a feeling that you or your surroundings are moving, sensation of tingling or numbness, headache, drowsiness.

Cardiovascular: postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity: spontaneous bleeding under the skin, sensitivity to light, rash, red patches on the skin, fever, respiratory distress including pneumonitis, anaphylactic reactions.

Other: Muscle spasm, weakness, restlessness, transient blurred vision, thirst, frequent urination, fatigue.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Confusion		✓	
Uncommon	Allergic reactions (difficulty breathing or swallowing, rash or hives, redness, intense itching and burning swelling) anaphylactic reactions.			✓

Uncommon	Low blood pressure aggravated by change of position (may be exacerbated by alcohol, barbiturates, or narcotics).		✓		Uncommon	Chest pain			✓
					<p><i>This is not a complete list of side effects. If you have any unexpected effects after receiving ALDACTAZIDE, contact your doctor or pharmacist.</i></p>				
Uncommon	Unusual bruising or bleeding		✓		HOW TO STORE IT				
Uncommon	Enlarged or painful breasts		✓		Store the medicine at room temperature 15 to 25°C;				
Uncommon	Fever	✓			Keep all medicines out of the reach and sight of children.				
Uncommon	Irregular menstrual period		✓		REPORTING SUSPECTED SIDE EFFECTS				
Uncommon	Muscle weakness, cramps or spasms		✓		<p>You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:</p> <p>-----</p> <p>\$ Report online at www.healthcanada.gc.ca/medeffect</p> <p>\$ Call toll-free at 1-866-234-2345</p> <p>\$ Complete a Canada Vigilance Reporting Form and:</p> <p style="padding-left: 20px;">- Fax toll-free to 1-866-678-6789, or - Mail to: Canada Vigilance Program Health Canada Postal Locator 0701D Ottawa, Ontario K1A 0K9</p> <p style="text-align: center;">Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.</p>				
Uncommon	Rapid, slow or irregular heartbeat		✓		<p><i>NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.</i></p>				
Uncommon	Vomiting blood		✓		MORE INFORMATION				
Uncommon	Rapid, excessive weight loss		✓		<p>This document plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001</p> <p>This leaflet was prepared by Pfizer Canada Last revised: October 05, 2010 © Pfizer Canada Inc., 2010</p>				
Uncommon	Shortness of breath		✓						
Uncommon	Respiratory distress including pneumonitis.			✓					
Uncommon	Skin rash		✓						
Uncommon	Yellowing of the skin or eyes inflammation of the pancreas, inflammation or enlargement of salivary glands.		✓						
Uncommon	Stomach ulcer (burning pain in the gut, vomiting...)		✓						
Uncommon	Imbalance of minerals in the blood High sugar levels in the blood (hyperglycemia)		✓						
Uncommon	Blood problems (loss of energy, low blood platelet count, abnormally low white blood cell count, severe reduction in granulocytes, severe anemia due to destruction or depressed functioning of the bone marrow...).		✓						
Uncommon	Impaired sense of sight.		✓						