PRODUCT MONOGRAPH

PrMINT- SPIRONOLACTONE

(Spironolactone Tablets USP)

25 mg and 100 mg Tablets

Aldosterone Antagonist

Mint Pharmaceuticals Inc.
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Mississauga, Ontario
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PrMINT-SPIRONOLACTONE

Spironolactone Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	All Nonmedicinal Ingredients
Oral	Tablet 25 mg, 100mg	Lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, magnesium stearate, peppermint flavour, colloidal silicon dioxide, hypromellose, polyethylene glycol, titanium dioxide, iron oxide yellow, and iron oxide red.

INDICATIONS AND CLINICAL USE

MINT-SPIRONOLACTONE (spironolactone) is indicated for the following:

1. Primary Hyperaldosteronism

MINT-SPIRONOLACTONE (spironolactone) is a useful agent in the diagnosis of primary hyperaldosteronism. In the presence of hypokalemic alkalosis and hypertension, a diagnosis of primary hyperaldosteronism should be considered if both blood pressure (BP) and serum electrolytes return to normal following treatment with MINT-SPIRONOLACTONE.

MINT-SPIRONOLACTONE is useful in the pre-operative treatment of patients with primary hyperaldosteronism and for the maintenance therapy of such patients who decline surgery, or who are unsuitable for surgery.

2. Edematous Conditions

a) Congestive Heart Failure (CHF):
MINT-SPIRONOLACTONE is useful in the management of edema and sodium retention in CHF when the patient is only partially responsive to, or intolerant of, other therapeutic measures.
MINT-SPIRONOLACTONE may be used alone or with thiazides. It is indicated in patients with CHF taking digitalis when other therapies are considered inappropriate.

b) Cirrhosis of the Liver Accompanied by Edema and/or Ascites:
Aldosterone levels may be exceptionally high in this condition. MINT-SPIRONOLACTONE is indicated for maintenance therapy, in combination with bed rest and the restriction of fluid and sodium.

c) The Nephrotic Syndrome:
MINT-SPIRONOLACTONE is useful for inducing a diuresis in patients not responsive to glucocorticoid therapy (for the nephrotic syndrome), and not responding to other diuretics. However, MINT-SPIRONOLACTONE has not been shown to affect the basic pathological process.

3. Essential Hypertension

MINT-SPIRONOLACTONE is indicated, usually in combination with other drugs, for patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate. MINT-SPIRONOLACTONE alone has mild to moderate antihypertensive activity.

4. Hypokalemia

MINT-SPIRONOLACTONE is indicated for treatment of hypokalemia, when other measures are considered inappropriate or inadequate. It is also indicated for the prophylaxis of hypokalemia in digitalis therapy when other measures are inadequate or inappropriate.

CONTRAINDICATIONS

MINT-SPIRONOLACTONE is contraindicated in:

- Patients who are hypersensitive to spironolactone, or to any ingredient in the formulation. For a complete listing, see the **Dosage Forms, Composition and Packaging Section**.
- Patients with anuria
- Patients with Addison's disease
- Patients with acute renal insufficiency or with severe impairment of renal function (GFR < 30 mL/Min/1.73 m^2)
- Patients with hyperkalemia
- Women who are pregnant
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women)
- Combination with eplerenone (see **Warnings and Precautions- Hyperkalemia, Drug Interactions sections**)
- Combination with heparin, low molecular weight heparin (see **Warnings and Precautions- Hyperkalemia, Drug Interactions sections**)

WARNINGS AND PRECAUTIONS

Avoid potassium supplements, salt substitutes and foods containing high levels of potassium (e.g., bananas, prunes, raisins and orange juice). Follow your doctor's directions for a low-salt or low-sodium diet and daily exercise program.

General

Use only for "Indications": Use MINT-SPIRONOLACTONE (spironolactone) 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. 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 MINT-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 when renal function is normal. 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 spironolactone.

Hematologic

Electrolyte Balance: Because of the diuretic action of MINT-SPIRONOLACTONE patients should be carefully evaluated for possible disturbance of fluid and electrolyte balance, due to the

possibility of hyperkalemia, hypochloremic alkalosis, hyponatremia and possible blood urea nitrogen (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 MINT-SPIRONOLACTONE if the potassium intake is excessive. This can cause cardiac irregularities, some of which may be fatal. Hyperkalemia may also occur even in the absence of potassium supplementation, particularly in patients with impaired renal function, elderly patients, or patients with diabetes. Consequently, no potassium supplementation should ordinarily be given with MINT-SPIRONOLACTONE. MINT-SPIRONOLACTONE should not be administered concurrently with other potassium-sparing diuretics. Spironolactone, when used with angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, Angiotensin II antagonists, other aldosterone blockers, even in the presence of a diuretic, has been associated with severe hyperkalemia (See **Drug Interactions** section).
Concomitant use of spironolactone with heparin, low molecular weight heparin, or other drugs or conditions known to cause hyperkalemia, may lead to severe hyperkalemia (See **Contraindications**, **Drug Interactions** section).

Hyperkalemia in Patients with Moderate to Severe Heart Failure

As hyperkalemia may be fatal, it is critical to monitor and manage serum potassium in patients with heart failure receiving MINT-SPIRONOLACTONE. 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 MINT-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 in Patients with Diabetes
Diabetic patients who are treated with MINT-SPIRONOLACTONE should also be treated with caution as they have an increased risk of hyperkalemia. The status of the patient's renal function and serum potassium levels should be assessed prior to initiating treatment and repeated within a few days and a few weeks thereafter in the patient at risk, especially in elderly patients. 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.

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. MINT-SPIRONOLACTONE should be discontinued and potassium intake (including dietary potassium) restricted.

b) Hyponatremia

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

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

Hepatic/Biliary/Pancreatic

Impaired Hepatic Function: MINT-SPIRONOLACTONE should be used with caution in patients with impaired hepatic function because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Management of Cirrhosis: Although high doses of MINT-SPIRONOLACTONE are required to treat edema and ascites in patients with cirrhosis, the drug dosage may be decreased before diuresis is complete to avoid the possibility of dehydration.

Neurologic: Lithium generally should not be given with diuretics (See **DRUG INTERACTIONS**).

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.

Special Populations

Pregnant Women: Spironolactone and its metabolites do cross the placental barrier. There are no studies in pregnant women. Therefore, the use of MINT-SPIRONOLACTONE requires that the potential benefits be weighed against the possible hazard to the mother and fetus.

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: see CONTRAINDICATIONS

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

Monitoring and Laboratory Tests

General: MINT-SPIRONOLACTONE therapy may cause transient elevation of BUN, especially in patients with 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.

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 following adverse reactions have been reported in association with spironolactone:

Blood and lymphatic system disorders: Leukopenia (including agranulocytosis), thrombocytopenia, anemia.

Gastrointestinal disorders*:* Diarrhea and cramping, gastric bleeding, gastritis, nausea, ulceration, vomiting.

General disorders and administration site conditions*:* Malaise. ATAXIA

Hepatobiliary disorders*:* Abnormal hepatic function. A few cases of mixed cholestatic/hepatocellular toxicity, with one reported fatality, have been reported with

spironolactone administration.

Immune system disorders*:* Drug fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis, pruritus, rash.

Metabolism and nutrition disorders*:* Electrolyte disturbances, hyperkalemia.

Musculoskeletal and connective tissue disorders: Leg cramps, muscle spasms, rhabdomyolysis, myalgia, weakness

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

Renal and urinary disorders: Renal dysfunction (including acute renal failure).

Reproductive system and breast disorders: gynecomastia* (see WARNINGS and PRECAUTIONS-Carcinogenesis and Mutagenesis), erectile dysfunction (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 male patients)

Respiratory, thoracic and mediastinal disorders: Dysphonia, dyspnea.

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, hypertrichosis.

*Gynecomastia may develop with the use of spironolactone, and physicians should be advised of its possible occurrence. Development of gynecomastia is related to both dose and duration of therapy. If gynecomastia develops, discontinue the drug. Gynecomastia is usually reversible when spironolactone is discontinued, although in rare instances some breast enlargement may persist.

Adverse reactions are usually reversible upon discontinuation of the drug.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1 Established or Potential Drug-Drug Interactions

Spironolactone Drug Interaction	Effect	Clinical comment
Alcohol, barbiturates or narcotics	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Antipyrine	Spironolactone enhances the metabolism of antipyrine.	
Cholestyramine/ Ammonium Chloride	Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in	

Spironolactone Drug Interaction	Effect	Clinical comment
	patients given spironolactone concurrently with ammonium chloride or cholestyramine.	
Corticosteroids, and adrenocorticotropic hormone (ACTH)	Intensified electrolyte depletion, particularly hypokalemia, may occur.	Monitor serum potassium, and adjust medications, as required.
Diuretics and Antihypertensives	Although MINT-SPIRONOLACTONE may be administered concomitantly with diuretics and antihypertensives, the effect of MINT-SPIRONOLACTONE is additive. Hyperkalemia has been associated with the use of angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, 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 MINT-SPIRONOLACTONE is added to 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.	
Drugs known to cause hyperkalemia	Concomitant use of drugs known to cause hyperkalemia with spironolactone may result in severe hyperkalemia	
Lithium	Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Lithium generally should not be given with diuretics.
Norepinephrine	Spironolactone reduces the vascular responsiveness to norepinephrine.	Caution should be exercised in the management of patients subjected to regional or general anaesthesia while being treated with spironolactone.
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 underdigitalization.
Non-Steroidal Anti-Inflammatory Drugs	Nonsteroidal anti-inflammatory drugs such as ASA, mefenamic acid, and indomethacin may	However, it has been shown that ASA does not alter the effect of spironolactone on blood pressure,

Spironolactone Drug Interaction	Effect	Clinical comment
	attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins and have been shown to attenuate the diuretic action of spironolactone. Hyperkalemia has been associated with the use of indomethacin in combination with potassium-sparing diuretics.	serum electrolytes, urea nitrogen, or plasma renin activity in hypertensive patients. If combination use is necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustment may be required.

Drug-Food Interactions

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 Cmax and $AUC_{(0-24)}$ of canrenone.

The clinical importance of this finding is not known.

Drug-Laboratory Test Interactions

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.

Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity (see **Drug-Drug Interactions**).

DOSAGE AND ADMINISTRATION

1. Diagnosis and Treatment of Primary Hyperaldosteronism

As an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets:

Long Test: Administer MINT-SPIRONOLACTONE at a daily dosage of 400 mg for 3-4 weeks. Correction of hypokalemia and hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short Test: Administer MINT-SPIRONOLACTONE at a daily dosage of 400 mg x 4 days. If serum potassium increases or urinary potassium decreases during MINT-SPIRONOLACTONE administration, but reverts when MINT-SPIRONOLACTONE is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

After the diagnosis of primary hyperaldosteronism has been established by more definitive testing

procedures, MINT-SPIRONOLACTONE may be administered in doses of 75 mg to 400 mg daily in preparation for surgery. For those unsuitable for surgery, spironolactone may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual.

2. Edematous Disorders Associated with Congestive Heart Failure, Cirrhosis and the Nephrotic Syndrome

When given as sole agent for diuresis, continue administration for at least 5 days. If an adequate response has been achieved within 5 days, continue dosage at the same level (or in selected patients, at a reduced dosage) in either single or divided daily doses. Some may respond adequately to a dosage of only 75 mg daily. If adequate diuresis is not obtained within 5 days, a second diuretic also should be given for additive effect. Occasionally for severe resistant edema, one may add a potent glucocorticoid to this combined therapy. Normally, an initial daily dosage of 100 mg (but may range from 25 mg to 200 mg daily) of MINT-SPIRONOLACTONE administered in either single or divided doses is recommended.

Dosage in Children: The initial daily dosage should provide approximately 3 mg/kg of body weight (1.5 mg/lb) administered in either single or divided doses. This dose should be reduced to 1-2 mg/kg for maintenance therapy or combination use with other diuretics.

3. Essential Hypertension

Usually in combination with other drugs, MINT-SPIRONOLACTONE is indicated for patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate. MINT-SPIRONOLACTONE has mild to moderate antihypertensive activity.

For adults an initial daily dosage of 50 mg/day to 100 mg/day (in either single or divided doses) of MINT-SPIRONOLACTONE is recommended. MINT-SPIRONOLACTONE may also be given with diuretics that act more proximally in the renal tubule or with other antihypertensive agents. Since a stabilized response may not occur before 2 weeks, continue treatment in either single or divided daily doses for that duration of time. Subsequently, adjust dosage in response to patient's needs. Most patients will respond to doses not exceeding 200 mg/day.

4. Hypokalemia

MINT-SPIRONOLACTONE in 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 inappropriate. See also Table 2 for a summary of dosage recommendations.

Table 2 MINT-SPIRONOLACTONE Dosage*

CONDITION	TYPE OF TEST	In single or Divided Daily Doses	
		INITIAL DOSAGE	MAXIMUM DOSAGE
Primary Hyperaldosteronism	Long Test	400 mg/day x 3-4 weeks	-
	Short Test	400 mg/day x	-

CONDITION	TYPE OF TEST	In single or Divided Daily Doses	
		INITIAL DOSAGE	MAXIMUM DOSAGE
		4 days	
	In preparation for Surgery	100-400 mg/day	400 mg/day
Edematous Disorders			
Congestive Heart Failure	-	100 mg/day	200 mg/day
Cirrhosis	Urinary: Na^+ / K^+ ratio >1 Na^+ / K^+ ratio <1	100 mg/day 200-400 mg/day	100 mg/day 400 mg/day
Nephrotic Syndrome	-	100 mg/day	200 mg/day
Essential Hypertension	-	50-100 mg/day	200 mg/day
Hypokalemia	-	25-100 mg/day	100 mg/day

*Maintenance dosage should be individually determined, and may be lower than the recommended initial dose.

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, mental confusion, diarrhea, or a maculopapular or erythematous rash. These manifestations disappear promptly on discontinuation of medication. Hyperkalemia may be exacerbated.

Treatment: No specific antidote. No persistent toxicity has occurred or is expected. Inducing vomiting and evacuating the stomach by lavage could be considered. Spironolactone use should be discontinued and potassium intake (including dietary sources) restricted.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action: Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent, sodium-potassium exchange site in the distal convoluted renal tubule. Spironolactone causes increased amounts of sodium and water to be excreted, while potassium loss is minimized.

Spironolactone 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.

Pharmacodynamics: Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for the edema and

ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by diuretic therapy.

Spironolactone is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism. It is also effective in most cases of essential hypertension, despite the fact that aldosterone secretion may be within normal limits in benign essential hypertension.

Through its action in antagonizing the effect of aldosterone, spironolactone inhibits the exchange of sodium for potassium in the distal renal tubule and helps to prevent potassium loss.

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

Pharmacokinetics: Spironolactone is rapidly and extensively metabolized to a number of metabolites including canrenone and the sulfur-containing 7-thiomethylspirolactone, 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 Spironolactone's Pharmacokinetic Parameters in Healthy Volunteers Administered 100 mg daily for 15 days.

	Mean C_{max} (ng/mL)	**Mean T_{max} (h)**	**Mean Post-Steady State $t_{½}$ (h)**	**Accumulation Factor: $AUC_{0\text{-}24\ h,\ Day\ 15}$ / $AUC_{0\text{-}24\ h,\ Day\ 1}$**
7-α-(thiomethyl) spirolactone (TMS)	391	3.2	13.8	1.25
6-β-hydroxy-7-α-(thiomethyl) spirolactone (HTMS)	125	5.1	15.0	1.50
Canrenone (C)	181	4.3	16.5	1.41
Spironolactone	80	2.6	~1.4 ($t_{½}$ β)	1.30

Special Populations

Hepatic Insufficiency

No pharmacokinetic studies have been performed with spironolactone in patients with hepatic insufficiency. Caution is advised in patients with hepatic impairment (see WARNINGS AND PRECAUTIONS – Hepatic/biliary/pancreatic section).

Renal Insufficiency

No pharmacokinetic studies have been performed with spironolactone in patients with renal insufficiency. MINT-SPIRONOLACTONE is contraindicated in patients with anuria, acute renal insufficiency or with severe impairment of renal function (GFR < 30 mL/Min/1.73 m^2) (see CONTRAINDICATIONS).

Elderly

No pharmacokinetic studies have been performed with spironolactone in the elderly population. Caution is advised in patients with hepatic and/or renal impairment (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – Hepatic/biliary/pancreatic section).

Pediatrics

No pharmacokinetic studies have been performed with spironolactone in the pediatric population. Therefore, safety and effectiveness in pediatric patients have not been established.

STORAGE AND STABILITY

Store between 15°C to 30°C in tight, light resistant containers.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MINT-SPIRONOLACTONE 25 mg:
Yellow coloured, film coated, round shaped, biconvex tablet with peppermint odour, debossed with "25" on one side and plain on the other side.

Non-medicinal ingredients include: Lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, magnesium stearate, peppermint flavor, colloidal silicon dioxide, hypromellose, polyethylene glycol, titanium dioxide, iron oxide yellow, and iron oxide red.

Available in bottles of 100 tablets and 500 tablets.

MINT-SPIRONOLACTONE 100 mg:

Peach coloured, film coated, round shaped, biconvex tablet with peppermint odour, debossed with "S" and "100" separated by a score line on one side and 'mint leaf art' on the other side.

Non-medicinal ingredients include: Lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, magnesium stearate, peppermint flavor, colloidal silicon dioxide, hypromellose, polyethylene glycol, titanium dioxide, iron oxide yellow, and iron oxide red.

Available in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

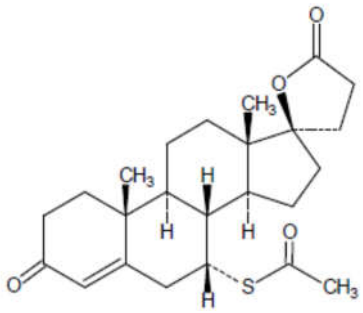
Proper name: spironolactone

Chemical name: 17-hydroxy-7α-mercapto-3-oxo-17α- pregn-4-ene-21-carboxylic acid γ-lactone acetate

Molecular formula: $C_{24}H_{32}O_4S$

Molecular mass: 416.6 g/mol

Structural formula:



Description: Spironolactone is a white or yellowish-white crystalline powder. It is practically insoluble in water, freely soluble in chloroform and soluble in alcohol.

CLINICAL TRIALS

A single-dose, two-treatment, two-way crossover, oral comparative bioavailability study of MINT-SPIRONOLACTONE 100 mg of Mint Pharmaceuticals Inc., and ALDACTONE™ (Spironolactone Tablets, USP) 100 mg of Pfizer Canada Inc, in healthy, adult male subjects under fasting conditions (n=47) was conducted.

Spironolactone (1 x 100 mg) From measured data Geometric Mean Arithmetic Mean (CV %)

Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng*hr/mL)	177.6 206.8 (53.6)	190.9 212.4 (46.8)	93.0%	83.8 to 103.3%
AUC_I (ng*hr/mL)	185.2 215.2 (53.2)	199.1 220.6 (45.8)	93.0%	83.7 to 103.4%
C_{MAX} (ng/mL)	58.6 69.2 (58.0)	71.4 81.5 (58.7)	81.8%	73.0 to 91.7%
T_{MAX}§ (h)	1.0 (0.5-5.0)	1.5 (0.5-4.5)		
$T_{½}$ € (h)	5.7 6.2 (41.9)	5.9 6.7 (53.4)		

* MINT-SPIRONOLACTONE 100 mg tablets (Mint Pharmaceuticals Inc.)

† ALDACTONE™ (Spironolactone Tablets, USP) 100 mg (Pfizer Canada Inc.) purchased in Canada

§ Expressed as the median (range)

€ Expressed as the arithmetic mean (CV%) only

Ascites:

Available studies suggest that spironolactone (100 to 400 milligrams (mg) daily) is effective for treating cirrhotic ascites in nonazotemic patients; an initial dose of 100 to 200 mg/day as a single dose has been recommended. Some patients may require doses of up to 1000 mg/day. When administered in doses of 300 to 600 mg/daily, 50% to 90% of patients achieve a satisfactory diuresis, suggesting hyperaldosteronism plays an important role in the pathogenesis of ascites in cirrhotic patients. Spironolactone should be avoided in patients with renal impairment, due to the risk of hyperkalemia.

Congestive Heart Failure:

In patients with severe congestive heart failure the addition of spironolactone to standard therapy (eg, ACE inhibitors, digoxin, thiazide and loop diuretics) significantly reduces morbidity (ie,

reduced hospitalization rate, improvement in symptoms) and mortality. Spironolactone improves exercise capacity and left ventricular volumes and systolic function (ie, ejection fraction) in patients with heart failure already on standard therapy including an ACE inhibitor at the maximal tolerated dose. The combination of spironolactone and ACE inhibitors is effective in the treatment of heart failure; however, the combination should not be used in patients with renal insufficiency and hyperkalemia.

Spironolactone improves exercise capacity and left ventricular (LV) volumes and systolic function in patients with heart failure (HF) already on standard treatment including an ACE inhibitor at the maximal tolerated dose. Left atrial end-systolic volume significantly decreased in patients given spironolactone compared with baseline ($p < 0.01$). LV ejection fraction significantly improved in patients given spironolactone and did not change in the control group (treatment group-by-time interaction, $p=0.02$). Peak oxygen consumption significantly decreased in the control group compared with baseline ($p < 0.001$) and did not change in the spironolactone group (treatment group-by-time interaction, $p < 0.05$). A dose-dependent effect was observed on LV ejection fraction and exercise capacity, with the greatest benefits from spironolactone in those patients treated with 50 mg/day. (See Tables 4 and 5)

Table 4 Summary of patient demographics for clinical trials in specific indication

Trial Design and duration	Dosage (mg/day), route of administration	Study subjects (n=number)	Mean age	Gender (male/female)
12 months, parallel, double-blind non-placebo controlled	-12.5-50 p.o. -Control group	n=106 patients treated with digitalis, diuretics and beta-blockers	62.1 ± 8.3	92/14

Table 5 Results of study in Congestive Heart Failure

Primary Endpoint	Associated value and statistical significance for spironolactone (mean 31.1 mg/day)	Associated value and statistical significance for active control
Effect on left ventricular (LV) function	LVEDV: B 275 ± 104 ml F-UP 251 ± 105 ml (p=0.06) LVESV: B 188 ± 94 ml F-UP 171 ± 97 ml (p=0.03)	LVEDV: B 257 ± 80 ml F-UP 253 ± 89 ml (p=NS) LVESV: B 173 ± 71 ml F-UP 168 ± 79 ml (p=NS)

B=baseline; F-UP= follow-up; LVEDV= left ventricular end-diastolic volume; LVESV= left ventricular end-systolic volume; NS= not statistically significant

In patients with severe congestive heart failure the addition of spironolactone to standard therapy significantly reduces morbidity and mortality. In the Randomized Aldactone Evaluation Study (RALES) study, patients with severe heart failure (New York Heart Association [NYHA] Class III - IV); left ventricular ejection fraction of no more than 35%) who were receiving standard therapy (ie, ACE inhibitor, loop diuretic, digoxin) were given either spironolactone or placebo. The study was stopped early, after a mean follow-up period of 24 months. There was a 30% reduction in the risk of death ($p < 0.001$). The reduction in the risk of death in the spironolactone group was attributed to a

lower risk of both death from progressive heart failure and sudden death from cardiac causes. The rate of hospitalization for worsening heart failure was 35% lower in the spironolactone group compared with the placebo group ($p < 0.001$). In addition, the rate of hospitalization for all cardiac causes was 30% lower in the spironolactone group compared with the placebo group ($p < 0.001$). The reductions in the risk of death and hospitalization were observed after 2 to 3 months of treatment and persisted throughout the study period. A significant improvement in the symptoms of heart failure ($p < 0.001$) occurred in patients who received spironolactone (41% of patients improved, 21% did not change, and 38% worsened) compared with placebo (33% of the patients improved, 18% did not change, and 48% worsened). Gynecomastia or breast pain occurred in 10% of the men in the spironolactone group and in 1% of the men in the placebo group ($p < 0.001$). The incidence of serious hyperkalemia was minimal and similar in both groups. (see Tables 6 and 7)

Table 6 Summary of patient demographics for RALES study in Congestive Heart Failure

Trial design and duration	Dosage (mg/day), route of administration	Study subjects (n= number)	Mean age (Range)	Gender (male/female) %
24 months, parallel, double- blind, placebo controlled	- 25-50 p.o. -placebo	1663 patients treated with ACE inhibitors, diuretics and digoxin in most cases	65 ± 12	73/27

Table 7 Results of RALES study in Congestive Heart Failure

Primary Endpoint	Associated value and statistical significance for spironolactone (mean 26 mg/day)	Associated value and statistical significance for active control
Death from any cause	284 deaths (35%) RR = 0.70, 95% CI: 0.60-0.82, P<0.001	386 deaths (46%)

The results of a study involving 214 patients with NYHA functional class II to IV congestive heart failure indicate that the addition of spironolactone to conventional therapy that includes ACE inhibitors, loop diuretics, and digoxin is safe and effective in blocking the effects of aldosterone. In addition to conventional therapy, patients were administered either placebo or spironolactone 12.5, 25, 50, or 75 milligrams once daily for 12 weeks. (see Table 8)

Table 8 Summary of patient demographics for RALES study in Congestive Heart Failure

Trial design and duration	Dosage (mg/day), route of administration	Study subjects (n=number)	Mean age (Range)	Gender (male/female) %
12-week, parallel, double- blind, placebo controlled	-12.5 p.o. -25 p.o. -50 p.o. -75 p.o. -placebo	214 patients treated with ACE inhibitors, diuretics +/- digoxin	63 ± 12 61 ± 9 62 ± 13 62 ± 13 61 ± 12 (placebo)	78/22 82/18 74/26 88/12 83/16 (placebo)

Compared to placebo, the addition of spironolactone produced statistically significant increases in plasma renin activity (PRA) and aldosterone excretion and decreases in blood pressure and pro-atrial natriuretic factor (ANF). Urinary aldosterone levels and PRA increased in a dose-dependent manner. Hypokalemia developed in 10% of patients given placebo and in 0.5% given spironolactone. The incidence of hyperkalemia increased with doses of spironolactone greater than or equal to 50 mg. Hyperkalemia developed in 5% of patients given placebo and in 5%, 13%, 20%, and 24% of patients given spironolactone 12.5, 25, 50, and 75 mg, respectively. There were no statistically significant changes in clinical status in spironolactone compared with placebo-treated patients.

Spironolactone administered to congestive heart failure (CHF) patients receiving normal doses of enalapril and furosemide caused an increase in serum magnesium and a decrease in ventricular arrhythmias. In a study involving 42 patients with NYHA functional class II or III CHF receiving enalapril (mean dose 17 mg/day) and furosemide (mean dose 72 mg/day), spironolactone 100 mg/day was administered causing statistically significant changes in the following parameters: increased plasma magnesium, decreased sodium retention, reduced urinary potassium and magnesium excretion, elevated plasma aldosterone and renin activity, and a reduction in ventricular premature contractions. (see Table 9)

Table 9 Summary of patient demographics for study in Congestive Heart Failure

Trial design and duration	Dosage (mg/day), route of administration	Study subjects (n= number)	Mean age (Range)	Gender (male/female) %
8 weeks, parallel, double- blind, placebo controlled	-50-100 p.o. -placebo	214 patients treated with ACE inhibitors and diuretics	68 ± 3 70 ± 2 (placebo)	22/6 10/4 (placebo)

A similar study of CHF showed that the addition of spironolactone 50 mg to 75 mg daily significantly reduced hourly premature ventricular complexes compared with baseline ($p < 0.0001$). Episodes of non-sustained ventricular tachycardia during exercise were reduced by 100% in the

spironolactone group and by 33% in the control group. Antagonism of aldosterone was thought to be an important mechanism in reducing these arrhythmias. (see Table 10)

Table 10 Summary of patient demographics for study in Congestive Heart Failure

Trial design and duration	Dosage (mg/day), route of administration	Study subjects (n= number)	Mean age (Range)	Gender (male/female)
20 weeks parallel, non- placebo controlled (4 weeks of observation +16 weeks treatment)	-50 p.o. X 12 weeks then 25 p.o. X 4 weeks -control group	35 patients treated with ACE inhibitors, diuretics and digoxin	48 ± 9	32/3

Hypertension:

Spironolactone is effective in the treatment of hypertension in doses of up to 400 mg/day with reduction in both standing and supine blood pressure with reported mean reduction values for systolic ranging from 20 to 30 mm Hg and for diastolic blood pressure 5 to 20 mm Hg or more. Spironolactone has been shown to be effective therapy for patients with refractory hypertension including African American and white patients, with or without primary aldosteronism, who are receiving multidrug regimens that include a diuretic and an ACE inhibitor or angiotensin receptor blocker (ARB). The antihypertensive effects of spironolactone persist for 1 to 2 weeks after discontinuation.

Low-dose spironolactone added-on to a multidrug regimen is effective in white and African American patients, with or without primary aldosteronism (PA), with resistant hypertension. In this study, patients receiving a multidrug regimen that included a diuretic and an ACE inhibitor or ARB were given spironolactone 12.5 to 50 mg daily as add-on therapy in order to achieve a further reduction in blood pressure (BP). (see Table 11)

Table 11 Summary of patient demographics for study in Hypertension

Trial design and duration	Dosage (mg/day), route of administration	Study subjects (n= number)	Mean age (Range)	Gender (male/female)
6- month, parallel, double- blind,	-12.5-50 p.o.	76 patients treated with ACE inhibitors or ARBs and diuretics	55 ± 12	31/45

At the 6-month follow-up, spironolactone produced an additional mean reduction in BP to a similar extent in African American and white patients with or without PA (mean decrease in systolic and diastolic BP, 25 and 12 mm Hg, respectively). The BP response was also similar in patients receiving an ACE inhibitor or an ARB. The mean number of antihypertensives decreased significantly from baseline to the 6-month follow-up ($p<0.05$) in patients with or without PA. It

should be noted that patients with PA were more likely to have spironolactone titrated up to 50 mg/day.

Spironolactone is safe and effective in the treatment of refractory hypertension. This prospective study involved 25 patients (ages 51 to 89 years) with refractory hypertension (hypertension of greater than 6 months duration; blood pressure (BP) greater than 140/90 mm Hg despite treatment with at least 2 antihypertensive agents given at optimal dosage). Spironolactone was added to the previous regimen at a dosage of 1 mg/kg/day. The dosage of spironolactone was reduced as soon as normalization of BP was achieved. (see Table 12)

Table 12 Summary of patient demographics for study in Hypertension

Trial design and duration	Dosage, route of administration	Study subjects (n= number)	Mean age (Range)	Gender (male/female)
3- month open-label	1 mg/kg/day p.o.	25	65 ± 11 (51-89)	10/15

For patients receiving an ACE inhibitor, this agent was replaced by spironolactone. Following 1 month of treatment with spironolactone, 23 patients achieved a BP of < 140/90 mm Hg. The 2 remaining patients achieved a BP of <140/90 mm Hg by 2 months. After 3 months of therapy with spironolactone, the mean number of antihypertensive agents required per patient significantly decreased from 3.2 to 2.1 ($p < 0.001$) including 5 patients who achieved adequate BP control with spironolactone monotherapy.

Hypokalemia:
Spironolactone produced significant dose-related increases in plasma potassium and aldosterone, and reductions in plasma sodium and bicarbonate in 15 hypertensive patients taking a diuretic. There was variability in response.

Nephrotic Syndrome:
Spironolactone is useful for inducing diuresis in edematous patients with nephrotic syndrome when glucocorticoid therapy is not effective. However, spironolactone does not affect the basic pathological process of the disease.

TOXICOLOGY

Acute Toxicity of Spironolactone:

Species	Route	LD_{50} ± Standard Error (mg/kg)
Mouse	Intragastric Intraperitoneal	>1000 356 ± 94
Rat	Intragastric Intraperitoneal	>1000 786 ± 125
Rabbit	Intragastric Intraperitoneal	>1000 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 ALT in males and females. Hypertrophy of thyroid and adrenal glands. Increase in hypertrophy of FSH cells. Mammary 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,

Species/ Number	Length of Study	Dose (mg/kg/d)	Results
			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.

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PART III: CONSUMER INFORMATION

[Pr]MINT-SPIRONOLACTONE
Spironolactone Tablets USP

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MINT-SPIRONOLACTONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MINT-SPIRONOLACTONE 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. It is also used to treat hyperaldosteronism (the body produces too much aldosterone, a naturally occurring hormone); and low potassium levels in the blood (hypokalemia).

What it does:

Spironolactone belongs to a class of medications called aldosterone receptor antagonists. It causes the kidney to eliminate unneeded water and sodium from the body into the urine, but reduces the loss of potassium from the body. This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking MINT-SPIRONOLACTONE regularly even if you feel fine. Do not stop taking MINT-SPIRONOLACTONE without talking to your doctor.

When it should not be used:

Do not take MINT-SPIRONOLACTONE if you:

- Are allergic to spironolactone or hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- Have difficulty urinating or produce no urine.
- Have kidney disease or Addison's disease
- Have high levels of potassium (hyperkalemia) in your blood
- Are pregnant
- Are breastfeeding. Spironolactone passes into breast milk.
- Are taking eplerenone (INSPRA)
- Are taking heparin or low molecular weight heparin used to prevent blood clotting

What the medicinal ingredient is:
Spironolactone.

What the nonmedicinal ingredients are:

Each MINT-SPIRONOLACTONE 25 mg and 100 mg tablet contains: Lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, magnesium stearate, peppermint flavour, colloidal silicon dioxide, hypromellose, polyethylene glycol, titanium dioxide, iron oxide yellow, and iron oxide red.

What dosage forms it comes in:

MINT-SPIRONOLACTONE 25 mg: Yellow coloured, film coated, round shaped, biconvex tablet with peppermint odour, debossed with "25" on one side and plain on the other side.

MINT-SPIRONOLACTONE 100 mg: Peach coloured, film coated, round shaped, biconvex tablet with peppermint odour, debossed with "S" and "100" separated by a score line on one side and 'mint leaf art' on the other side.

MINT-SPIRONOLACTONE tablets are available in 25 mg strength in bottles of 100 and 500 and 100 mg strength in bottles of 100.

WARNINGS AND PRECAUTIONS

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

Before you receive MINT-SPIRONOLACTONE, talk to your doctor, nurse, or pharmacist if you:

- Have diabetes, kidney disease or liver disease;
- Have or have ever had gout
- Are taking a Non-steroidal anti-inflammatory drugs (NSAIDs) used to reduce pain and swelling. Examples include Aspirin, ibuprofen (Advil, Motrin), naproxen (Aleve), and celecoxib (Celebrex)
- Are taking an angiotensin converting enzyme (ACE) inhibitor. You can recognize ACE inhibitors because their medicinal ingredient ends in "PRIL". It lowers blood pressure.
- Are taking an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN". It lowers blood pressure
- Are taking lithium used to treat bipolar disorder (manic-depressive illness)
- Are pregnant, plan to become pregnant, or are

breast feeding. If you become pregnant while taking MINT-SPIRONOLACTONE, call your doctor immediately;
- Are a man and develop tender or enlarged breast tissue
- Are having surgery, including dental surgery, and will be given an anesthetic. Be sure to tell the doctor or dentist that you are taking MINT-SPIRONOLACTONE.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to MINT-SPIRONOLACTONE. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is decreased (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.

DIETARY RESTRICTIONS

Follow your doctor's directions for a low-salt or low-sodium diet and daily exercise program. Avoid potassium-containing salt substitutes. Limit your intake of potassium-rich foods (eg, bananas, prunes, raisins, and orange juice). Ask your doctor for advice on how much of these foods you may have.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, nonprescription drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with MINT-SPIRONOLACTONE:

- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Corticosteroids used to treat joint pain and swelling.
- Digoxin, a heart medication
- Drugs that cause hyperkalemia (high levels of potassium in blood)
- Lithium used to treat bipolar disorder (manic-depressive illness)
- Nonsteroidal anti-inflammatory drugs (NSAIDs), use to reduce pain and swelling. Examples include Aspirin, ibuprofen, naproxen, and celecoxib.
- Other blood pressure lowering drugs, including diuretics. When taken in combination with MINT-SPIRONOLACTONE, they may cause excessively low blood pressure.

PROPER USE OF THIS MEDICATION

MINT-SPIRONOLACTONE comes as a tablet to take by mouth. Take it exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor. It usually is taken once a day in the morning with breakfast or twice a day with breakfast and lunch. Carefully follow your doctor's instructions about any special diet.

Missed Dose: Take the missed dose as soon as you remember it. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not take a double dose to make up for a missed one.

Overdose:

If you think you have taken too much MINT-SPIRONOLACTONE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Gastrointestinal: Constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth, indigestion, dryness of mouth, abdominal pain, and cramps.

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

Cardiovascular: low blood pressure while you are standing (postural hypotension), may be aggravated by alcohol, barbiturates, or narcotics.

Hypersensitivity: Fever, difficulty breathing anaphylactic reactions

Musculoskeletal: Muscle cramps, spasms, and pain, weakness, restlessness

Psychiatric: Reduced libido

Reproductive: In men: breast swelling, difficulty in getting or maintaining erections. In women: breast discomfort, irregular or missed menstrual periods, postmenopausal bleeding.

Skin: Bleeding under the skin, rash, red patches on the skin.

Other: Thirst, frequent urination, and fatigue.

If any of these affect you severely, tell your doctor, nurse or pharmacist

MINT-SPIRONOLACTONE can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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 seek immedi-ate medical help
		Only if severe	In all cases	
Common	**Low Blood Pressure**: Dizziness, fainting, lightheaded-ness. May occur when you go from sitting to standing up (may be exacerbated by alcohol, barbiturates or narcotics).	✓		
	Decreased levels of potassium in the blood: Irregular heartbeats, muscle weakness and generally feeling unwell		✓	
Uncommon	**Allergic Reaction:** Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, redness, intense itching and burning, anaphylactic reactions			✓
	Kidney Disorder: Change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
	Liver Disorder: Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Increased Blood Sugar: Frequent urination, thirst and hunger	✓		

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 seek immedi-ate medical help**
		Only if severe	**In all cases**	
	Electrolyte Imbalance: Weakness, drowsiness, muscle pain or cramps, rapid, slow or irregular heartbeat		✓	
	Confusion		✓	
	Enlarged or painful breasts in men		✓	
	Fever	✓		
	Vomiting blood		✓	
	Rapid, excessive weight loss		✓	
	Shortness of breath		✓	
	Skin rash		✓	
	Yellowing of the skin or eyes		✓	
	Stomach ulcer (burning pain in the gut, vomiting)		✓	
	Blood problems (loss of energy, severe anemia)		✓	
	Chest pain, difficulty breathing			✓
Rare	**Decreased Platelets:** Bruising, bleeding, fatigue and weakness		✓	
	Decreased		✓	

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 seek immedi-ate medical help**
		Only if severe	**In all cases**	
	White Blood Cells: Infections, fatigue, fever, aches, pains, and flu-like symptoms			
Very rare	**Toxic Epidermal Necrolysis:** Severe skin peeling, especially in mouth and eyes			✓
Unknown	**Anemia:** Fatigue, loss of energy, weakness, shortness of breath		✓	
	Inflammation of the Pancreas: Abdominal pain that lasts and gets worse when you lie down, nausea and vomiting		✓	

This is not a complete list of side effects. If you have any unexpected effects after receiving MINT-SPIRONOLACTONE, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store between 15°C to 30°C in tight, light resistant containers.

Keep MINT-SPIRONOLACTONE out of reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

Note: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about MINT-SPIRONOLACTONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for health professionals and includes this Consumer Information by the visiting Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (http://www.mintpharmaceuticals.com), or by calling 1-877-398-9696.

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