

PRODUCT MONOGRAPH

PrNTP-SPIRONOLACTONE

(Spironolactone Tablets, USP)

25 mg and 100 mg Tablets

Aldosterone Antagonist

NT Pharma Canada Limited
5691 Main Street
Stouffville, Ontario
Canada, L4A 1H5

Date of Preparation:
March 26, 2010

Control #: 137214

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PrNTP-SPIRONOLACTONE
Spironolactone Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablets 25 mg and 100 mg	Lactose monohydrate <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

NTP-SPIRONOLACTONE 25 mg: cream coloured, round, bi-convex, peppermint odour, compressed tablets, engraved 2 vertical bisect 5 on one side and modified N on the reverse.

NTP-SPIRONOLACTONE 100 mg: cream coloured, round, bi-convex, peppermint odour, compressed tablets, engraved modified N vertical bisect N on one side and 100 on the reverse.

INDICATIONS AND CLINICAL USE

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

1. Primary Hyperaldosteronism

NTP-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 NTP-SPIRONOLACTONE.

NTP-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):

NTP-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. NTP-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. NTP-SPIRONOLACTONE is indicated for maintenance therapy, in combination with bed rest and the restriction of fluid and sodium.

c) The Nephrotic Syndrome:

NTP-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, NTP-SPIRONOLACTONE has not been shown to affect the basic pathological process.

3. Essential Hypertension

NTP-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. NTP-SPIRONOLACTONE alone has mild to moderate antihypertensive activity.

4. Hypokalemia

NTP-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

- Anuria
- Acute renal insufficiency
- Addison's disease
- Significant impairment of renal function
- Hyperkalemia
- Hypersensitivity to spironolactone or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section.

WARNINGS AND PRECAUTIONS

General

Use only for "Indications": Use NTP-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.

Endocrine and Metabolism

Gynecomastia: Gynecomastia may develop with the use of NTP-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.

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

Hematologic

Electrolyte Balance: Because of the diuretic action of NTP-SPIRONOLACTONE patients should be carefully evaluated for possible disturbance of fluid and electrolyte balance, due to the possibility of hyperkalemia, hyponatremia, 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 NTP-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 NTP-SPIRONOLACTONE. NTP-SPIRONOLACTONE should not be administered concurrently with other potassium-sparing diuretics. Spironolactone, when used with angiotensin converting enzyme (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 section). 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. NTP-SPIRONOLACTONE should be discontinued and potassium intake (including dietary potassium) restricted.

b) Hyponatremia

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

NTP-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: NTP-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 NTP-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 may cross the placental barrier. There are no studies in pregnant women. Therefore, the use of NTP-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: Canrenone, a major (and active) metabolite of spironolactone, appears 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: NTP-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:

Body as a Whole: Malaise.

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

Hematologic: Leukopenia (including agranulocytosis), thrombocytopenia, anemia.

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

Liver/biliary: Hepatic function disorder. A very few cases of mixed cholestatic/hepatocellular toxicity, with one reported fatality, have been reported with spironolactone administration.

Metabolism: Electrolyte disturbances, hyperkalemia

Musculoskeletal: Leg cramps.

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

Renal: Renal dysfunction (including acute renal failure).

Reproduction: Abnormal semen (decreased motility and sperm count), inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, benign breast neoplasm, breast pain.

Carcinoma of the breast has been reported in patients, including male patients, taking spironolactone, but a cause and effect relationship has not been established.

Respiratory: Dysphonia, dyspnea.

Skin and appendages: Alopecia, hypertrichosis

Gynecomastia may develop in association with the use of spironolactone. Development of gynecomastia is related to both dose and duration of therapy. 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	Potential of orthostatic hypotension may occur.	
Antipyrene.	Spironolactone enhances the metabolism of	

Spironolactone Drug Interaction	Effect	Clinical comment
	antipyrene.	
Cholestyramine/ Ammonium Chloride	Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, 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 NTP-SPIRONOLACTONE may be administered concomitantly with diuretics and antihypertensives, the effect of NTP-SPIRONOLACTONE is additive. 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 NTP-SPIRONOLACTONE is added to the regimen.
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	NTP-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	ASA, mefenamic acid, and indomethacin may attenuate the diuretic action of spironolactone 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.

Drug-Food Interactions

Food increases the bioavailability of unmetabolized spironolactone (two 100 mg NTP-SPIRONOLACTONE tablets) by almost 100%. 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 NTP-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 NTP-SPIRONOLACTONE at a daily dosage of 400 mg x 4 days. If serum potassium increases or urinary potassium decreases during NTP-SPIRONOLACTONE administration, but reverts when NTP-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, NTP-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 25-200 mg daily) of NTP-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, NTP-SPIRONOLACTONE is indicated for patients who cannot be treated adequately with other agents or for whom other agents are considered inappropriate. NTP-SPIRONOLACTONE has mild to moderate antihypertensive activity.

For adults an initial daily dosage of 50-100 mg (in either single or divided doses) of NTP-SPIRONOLACTONE is recommended. NTP-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

NTP-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: NTP-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 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	100 mg/day	100 mg/day
	Na ⁺ / K ⁺ ratio <1	200-400 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.

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.

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

Pharmacokinetics: Spirolactone 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 spirolactone. In the dose range of 25 mg to 200 mg, an approximately linear relationship exists between a single dose of spirolactone 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 spirolactone, 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 spirolactone and canrenone are more than 90-percent bound to plasma proteins. The metabolites of spirolactone are excreted both in the urine (32-53%), and through biliary excretion in the feces (14-36%).

Table 3: Summary of Spirolactone’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 _{1/2} (h)	Accumulation Factor: AUC _{0-24 h, Day 15} / AUC _{0-24 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
Spirolactone	80	2.6	~1.4 (t _{1/2} β)	1.30

STORAGE AND STABILITY

Store between 15°C -30°C. Protect from light and humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NTP-SPIRONOLACTONE 25 mg:

Each cream coloured, round, bi-convex, peppermint odour, compressed tablets, engraved 2 vertical bisect 5 on one side and modified N on the reverse contains Spironolactone 25 mg.

Non-medicinal ingredients include: D&C Yellow # 10, FD&C Yellow # 6, lactose monohydrate, natural peppermint flavour, magnesium stearate, sodium lauryl sulfate and sodium starch glycolate.

Available in bottles of 100, tablets.

NTP-SPIRONOLACTONE 100 mg:

Each cream coloured, round, bi-convex, peppermint odour, compressed tablets, engraved modified N vertical bisect N on one side and 100 on the reverse contains Spironolactone 100 mg.

Non-medicinal ingredients include: D&C Yellow # 10, FD&C Yellow # 6, lactose monohydrate, natural peppermint flavour, magnesium stearate, sodium lauryl sulfate and sodium starch glycolate.

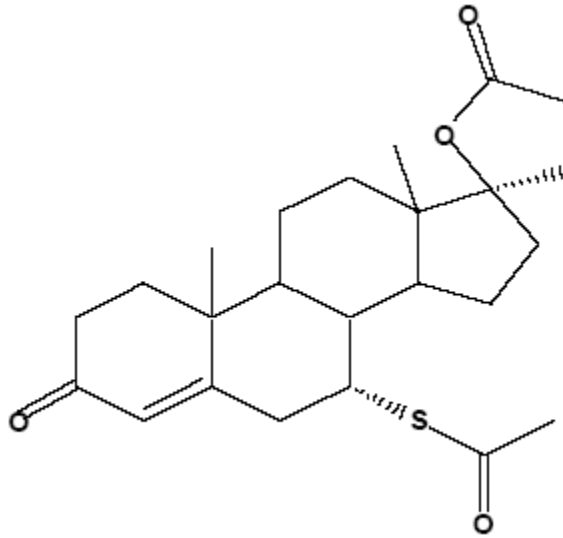
Available in bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	spironolactone
Chemical name:	17-Hydroxy-7a-mercapto-3-oxo-17a-pregn-4-ene-21-carboxylic acid, g-lactone acetate
Molecular formula:	$C_{24}H_{32}O_4S$
Molecular mass:	416.6
Structural formula:	



Description: Spironolactone is an off-white, micronized powder with a slightly bitter taste. It is practically insoluble in water, soluble in chloroform, ethanol, ethyl acetate, and slightly soluble in methanol.

CLINICAL TRIALS

A comparative study was carried out in 12 volunteers on two 25 mg spironolactone tablet products, NTP-Spironolactone 25 mg manufactured by Novopharm Limited and Aldactone® 25 mg formulated by G.D. Searle Canada Ltd.

Six subjects were administered 8 NTP-Spironolactone 25 mg tablets (200 mg spironolactone) and 6 received 8 Aldactone® 25 mg tablets (200 mg spironolactone) with 240 mL of water. The subjects were fasted for 10 hours before and 4 hours after the administration of the drug. Blood samples for analysis were taken at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0 and 24 hours after the administration of the drug. Seven days later, the study was repeated with the subjects receiving the alternate product according to the standard crossover design. The plasma levels of canrenone, the principal spironolactone metabolite, were determined at each sampling time by a specific HPLC method. The pharmacokinetic data calculated for the NTP-Spironolactone and Aldactone® tablet formulations is tabulated below:

Plasma Canrenone	NTP-Spironolactone (Novopharm Limited)	Aldactone® (G.D. Searle Canada Limited)
AUC₀₋₂₄ (ng.h/ml)	2088.7 ± 560.3	2161.8 ± 601.3
C_{max} (ng/ml)	170.5 ± 42.2	185.0 ± 50.1
T_{max} (h)	3.3 ± 1.1	3.5 ± 0.7
T_{1/2} (h)	10.24 ± 2.03	9.43 ± 1.72
K_{el} (h⁻¹)	0.07 ± 0.02	0.08 ± 0.01

The mean relative bioavailability for NTP-Spironolactone tablets was 97.1 ± 10.9% of that for Aldactone® tablets.

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 Spironolactone Evaluation Study RALES) study, patients with severe heart failure (NYHA class III or 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.	214 patients treated with ACE inhibitors, diuretics +/- digoxin	63 ± 12	78/22
	-25 p.o.		61 ± 9	82/18
	-50 p.o.		62 ± 13	74/26
	-75 p.o.		62 ± 13	88/12
	-placebo		61 ± 12 (placebo)	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	>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 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, atrophy of the prostate gland and hyperplasia of zona glomerulosa of the adrenal gland.
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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

NTP-SPIRONOLACTONE

spironolactone tablets

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 NTP-SPIRONOLACTONE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- Fluid retention (edema) caused by various conditions, including heart disease, cirrhosis of the liver and nephrotic syndrome;
- High blood pressure;
- Hyperaldosteronism (the body produces too much aldosterone, a naturally occurring hormone);
- Low potassium levels in the blood (hypokalemia).

What it does:

Spironolactone is in 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.

When it should not be used:

You should not use this medicine if you have had an allergic reaction to spironolactone, or if you have certain kidney diseases, high levels of potassium in your blood (hyperkalemia), or if you are pregnant or unable to urinate.

What the medicinal ingredient is:

Spironolactone.

What the important nonmedicinal ingredients are:

Each NTP-SPIRONOLACTONE 25 mg and 100 mg tablet contains: D&C Yellow # 10, FD&C Yellow # 6, lactose monohydrate, natural peppermint flavour, magnesium stearate, sodium lauryl sulfate and sodium starch glycolate.

What dosage forms it comes in:

NTP-SPIRONOLACTONE 25 mg: cream coloured, round, bi-convex, peppermint odour, compressed tablets, engraved 2 vertical bisect 5 on one side and modified N on the reverse.

NTP-SPIRONOLACTONE 100 mg: cream coloured, round, bi-convex, peppermint odour, compressed tablets, engraved modified N vertical bisect N on one side and 100 on the reverse.

Avoid potassium supplements and foods containing high levels of potassium including salt substitutes.

WARNINGS AND PRECAUTIONS

Before taking NTP-SPIRONOLACTONE,

- tell your doctor and pharmacist if you are allergic to spironolactone, sulfa drugs, or any other drugs;
- tell your doctor and pharmacist what prescription and nonprescription medications you are taking, especially aspirin; lithium; medications for arthritis, diabetes, or high blood pressure; potassium supplements; and vitamins;
- tell your doctor if you have or have ever had diabetes, gout, or kidney or liver disease;
- tell your doctor if you are pregnant, plan to become pregnant, or are breast feeding. If you become pregnant while taking spironolactone, call your doctor immediately;
- if you are having surgery, including dental surgery, tell the doctor or dentist that you are taking spironolactone;
- you should know that this drug may make you drowsy or dizzy. Do not drive a car or operate machinery, or do anything else that could be dangerous if you are not alert 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

Drugs that may interact with NTP-SPIRONOLACTONE include: aspirin, lithium, digoxin, antipyrine, cholestyramine, and medications for arthritis, diabetes, or high blood pressure.

ABOUT THIS MEDICATION

NTP-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.

IMPORTANT: PLEASE READ

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

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

- upset stomach
- abdominal pain
- frequent urination
- dryness of mouth, thirst

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	
Vomiting	✓		
Diarrhea	✓		
Dizziness	✓		
Headache	✓		
Drowsiness	✓		
Fatigue	✓		
Fever	✓		
Enlarged or painful breasts		✓	
Irregular menstrual period		✓	
Confusion		✓	
Muscle weakness or cramps		✓	
Rapid, excessive weight loss		✓	
Rapid, slow or irregular heartbeat		✓	
Shortness of breath		✓	
Unusual bruising or bleeding		✓	
Yellowing of the skin or eyes		✓	
Skin rash			✓
Vomiting blood			✓

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

HOW TO STORE IT

Store between 15°C-30°C. Protect from light and humidity.

Keep all medicines out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

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:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

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.

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, at NT Pharma Canada Limited at:
1-800-268-4127 ext. 5005
or druginfo@novopharm.com

This leaflet was prepared by:
NT Pharma Canada Limited
5691 Main Street
Stouffville, Ontario
Canada, L4A 1H5

Last revised: March 26, 2010