1. NAME OF THE MEDICINAL PRODUCT

Aldactone®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: spironolactone 25 mg.

3. PHARMACEUTICAL FORM

Tablets are for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spironolactone is indicated for the following:

- Congestive cardiac failure.
- Hepatic cirrhosis with ascites and edema.
- Malignant ascites.
- Nephrotic syndrome.
- Diagnosis and treatment of primary hyperaldosteronism.

4.2 Posology and method of administration

Administration of spironolactone once daily with a meal is recommended.

Adults
Congestive cardiac failure
The usual dosage is 100 mg/day. In difficult or severe cases, the dosage may be gradually increased up to 400 mg/day. When edema is controlled, the usual maintenance level is 75 mg/day to 200 mg/day.

Hepatic cirrhosis with ascites and edema
If urinary Na^+/K^+ ratio is greater than 1.0, the usual adult dose is 100 mg/day. If the ratio is less than 1.0, the usual adult dose is 200 mg/day to 400 mg/day. Maintenance dosage should be individually determined.

Malignant ascites
Initial dose is usually 100 mg/day to 200 mg/day. In severe cases the dosage may be gradually increased up to 400 mg/day. When edema is controlled, maintenance dosage should be individually determined.

Nephrotic syndrome
The usual adult dose is 100 mg/day to 200 mg/day. Spironolactone has not been shown to be anti-inflammatory, or to affect the basic pathological process. Its use is only advised if glucocorticoids by themselves are insufficiently effective.

Diagnosis and treatment of primary hyperaldosteronism
Spironolactone may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long test: Daily adult dose of 400 mg for 3 to 4 weeks. Correction of hypokalemia and hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

Short test: Daily dosage of 400 mg for 4 days. If serum potassium increases during spironolactone administration, but drops when spironolactone is discontinued, a presumptive diagnosis of primary hyperaldosteronism should be considered.

Short-term preoperative treatment of primary hyperaldosteronism
After the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, spironolactone may be administered at doses of 100 mg to 400 mg daily in preparation of surgery. For patients who are considered unsuitable candidates for surgery, Aldactone may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

Elderly
It is recommended that treatment is started with the lowest dose and titrated upwards as required to achieve maximum benefit. Care should be taken with severe hepatic and renal impairment which may alter drug metabolism and excretion.

Children
Initial dosage is 3 mg/kg body weight daily in divided doses. Dosage should be adjusted on the basis of response and tolerance. If necessary a suspension may be prepared by pulverizing spironolactone tablets with a few drops of glycerine and adding cherry syrup. Such a suspension is stable for one month when refrigerated at 2°C to 8°C.

4.3 Contraindications

Spironolactone is contraindicated in patients with the following:

- acute renal insufficiency, significant renal compromise, anuria;
- Addison's disease;
- hyperkalemia;
- hypersensitivity to spironolactone;
- concomitant use of eplerenone.

4.4 Special warnings and precautions for use

Concomitant use of spironolactone with other potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or other drugs or conditions known to cause hyperkalemia, potassium supplements, a

diet rich in potassium, or salt substitutes containing potassium, may lead to severe hyperkalemia. Hyperkalemia can cause cardiac irregularities which may be fatal. Should hyperkalemia develop, spironolactone should be discontinued, and if necessary, active measures taken to reduce the serum potassium to normal.

Periodic estimation of serum electrolytes is recommended due to the possibility of hyperkalemia, hyponatremia and possible transient blood urea nitrogen (BUN) elevation, especially in the elderly and/or in patients with pre-existing impaired renal or hepatic function. Hyponatremia may be induced especially if spironolactone is administered in combination with other diuretics.

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

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

4.5 Interactions with other medicinal products and other forms of interaction

Concomitant use of drugs known to cause hyperkalemia with spironolactone may result in severe hyperkalemia.

Spironolactone may have an additive effect when given concomitantly with other diuretics and antihypertensive agents. The dose of such drugs may need to be reduced when spironolactone is added to the treatment regimen.

Spironolactone reduces vascular responsiveness to noradrenaline. Caution should be exercised in the management of patients subjected to regional or general anesthesia while they are being treated with spironolactone.

Spironolactone has been reported to increase serum digoxin concentration and to interfere with certain serum digoxin assays. In patients receiving digoxin and spironolactone the digoxin response should be monitored by means other than serum digoxin concentrations, unless the digoxin assay used has been proven not to be affected by spironolactone therapy. If it proves necessary to adjust the dose of digoxin, patients should be carefully monitored for evidence of enhanced or reduced digoxin effect.

NSAIDs such as aspirin, indomethacin, and mefenamic acid may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins and have been shown to reduce the diuretic effect of spironolactone. Combination of NSAIDs with potassium-sparing diuretics has been associated with severe hyperkalemia.

Spironolactone enhances the metabolism of antipyrine.

Hyperkalemic metabolic acidosis has been reported in patients given spironolactone concurrently with ammonium chloride or cholestyramine.

Co-administration of spironolactone with carbenoxolone may result in decreased efficacy of either agent.

Spironolactone binds to the androgen receptor and may increase prostate-specific antigen (PSA) levels in abiraterone-treated prostate cancer patients. Use with abiraterone is not recommended.

4.6 Fertility, pregnancy and lactation

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

There are no studies in pregnant women. Spironolactone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Canrenone, a major (and active) metabolite of spironolactone, appears in human breast milk. Because many drugs are excreted in human milk and because of the unknown potential for adverse effects 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.

4.7 Effects on ability to drive and use machines

See section **4.4 Special warnings and precautions for use**.

4.8 Undesirable effects

The following adverse events have been reported in association with spironolactone therapy:

Table 1. Adverse Drug Reactions	
System Organ Class	**Adverse Drug Reactions**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Benign breast neoplasm (male)
Blood and lymphatic system disorders	Agranulocytosis, Leukopenia, Thrombocytopenia
Metabolism and nutrition disorders	Hyperkalemia, Electrolyte imbalance
Psychiatric disorders	Confusional state, Libido disorder
Nervous system disorders	Dizziness, Headache, Ataxia
Gastrointestinal disorders	Nausea, Gastrointestinal disorder
Hepatobiliary disorders	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Pruritus, Rash, Urticaria, Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Drug reaction with eosinophilia and systemic symptoms (DRESS), Alopecia, Hypertrichosis

Table 1. Adverse Drug Reactions	
System Organ Class	**Adverse Drug Reactions**
Musculoskeletal and connective tissue disorders	Muscle spasms
Renal and urinary disorders	Acute kidney injury
Reproductive system and breast disorders	Gynecomastia, Breast pain (male), Menstrual disorder, Breast pain (female)
General disorders and administration site conditions	Malaise

4.9 Overdose

Acute overdose may be manifested by nausea, vomiting, drowsiness, mental confusion, maculopapular or erythematous rash, or diarrhea. Hyponatremia or hyperkalemia may be induced but these effects are unlikely to be associated with acute overdosage. Symptoms of hyperkalemia may manifest as paresthesia, weakness, flaccid paralysis or muscle spasm and may be difficult to distinguish clinically from hypokalemia. Electrocardiographic changes are the earliest specific signs of potassium disturbances. No specific antidote has been identified. Improvement may be expected after withdrawal of the drug. General supportive measures including replacement of fluids and electrolytes may be indicated. For hyperkalemia, reduce potassium intake, administer potassium-excreting diuretics, intravenous glucose with regular insulin, or oral ion-exchange resins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 is retained. Spironolactone acts both as a diuretic and as an antihypertensive drug by this mechanism. It may be given alone or with other diuretic agents that act more proximally in the renal tubule.

Aldosterone antagonist activity
Increased levels of the mineralocorticoid, aldosterone, are present in primary and secondary hyperaldosteronism. Edematous states in which secondary aldosteronism is usually involved include congestive heart failure, hepatic cirrhosis, and the nephrotic syndrome. By competing with aldosterone for receptor sites, spironolactone provides effective therapy for edema and ascites in those conditions. Spironolactone counteracts secondary aldosteronism induced by the volume depletion and associated sodium loss caused by active 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.

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

5.2 Pharmacokinetic properties

Spironolactone is rapidly and extensively metabolized. Sulfur-containing products are the predominant metabolites and are thought to be primarily responsible, together with spironolactone, for the therapeutic effects of the drug. The following pharmacokinetic data were obtained from 12 healthy volunteers following the administration of 100 mg of spironolactone daily for 15 days. On the 15th day, spironolactone was given immediately after a low-fat breakfast and blood was drawn thereafter.

	Accumulation Factor: AUC (0-24 hours, Day 15)/AUC (0-24 hours, Day 1)	**Mean Peak Serum Concentration**	**Mean (SD) Post-steady-state Half-life**
7-α-(thiomethyl) spirolactone	1.25	391 ng/mL at 3.2 hours	13.8 hours (6.4) (terminal)
6-β-hydroxy-7-α-(thiomethyl) spirolactone	1.50	125 ng/mL at 5.1 hours	15.0 hours (4.0) (terminal)
Canrenone	1.41	181 ng/mL at 4.3 hours	16.5 hours (6.3) (terminal)
Spironolactone	1.30	80 ng/mL at 2.6 hours	Approximately 1.4 hours (0.5) (β half-life)

The pharmacological activity of spironolactone metabolites in man is not known. However, in adrenalectomized rats, the antimineralocorticoid activities of the metabolites canrenone (C), 7-α-(thiomethyl) spirolactone (TMS), and 6-β-hydroxy-7-α-(thiomethyl) spirolactone (HTMS), relative to spironolactone, were 1.10, 1.28, and 0.32, respectively. Relative to spironolactone, their binding affinities to the aldosterone receptors in rat kidney slices were 0.19, 0.86, and 0.06, respectively.

In humans, the potencies of TMS and 7-α-thiospirolactone in reversing the effects of the synthetic mineralocorticoid, fludrocortisone, on urinary electrolyte composition were 0.33 and 0.26, respectively, relative to spironolactone. However, since the serum concentrations of these steroids were not determined, their incomplete absorption and/or first-pass metabolism could not be ruled out as a reason for their reduced *in vivo* activities.

Spironolactone and its metabolites are more than 90% bound to plasma proteins. The metabolites are excreted primarily in the urine and secondarily in bile.

The effect of food on spironolactone absorption was assessed in a single-dose study of nine healthy, drug-free volunteers. Food increased the bioavailability of unmetabolized spironolactone by almost 100%. The clinical importance of this finding is not known.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Orally administered spironolactone has been shown to be a tumorigen in dietary administration studies performed in rats, with its proliferative effects manifested on endocrine organs and the liver. In an 18-month study using doses of about 50, 150 and 500 mg/kg/day, there were statistically significant increases in benign adenomas of the thyroid and testes and, in male rats, a dose-related increase in proliferative changes in the liver (including hepatocytomegaly and hyperplastic nodules). In 24-month studies in which rats were administered doses of about 10, 30, 100, and 150 mg/kg/day of spironolactone, the range of proliferative effects included significant increases in hepatocellular adenomas and testicular interstitial cell tumors in males, and significant increases in thyroid follicular cell adenomas and carcinomas in both sexes. There was also a statistically significant increase in benign uterine endometrial stromal polyps in females.

A dose-related (above 30 mg/kg/day) incidence of myelocytic leukemia was observed in rats fed daily doses of potassium canrenoate (a compound chemically similar to spironolactone and whose primary metabolite, canrenone, is also a major product of spironolactone in man) for a period of 1 year. In 2-year studies in the rats, oral administration of potassium canrenoate was associated with myelocytic leukemia and hepatic, thyroid, testicular and mammary tumors.

Neither spironolactone nor potassium canrenoate produced mutagenic effects in tests using bacteria or yeast. In the absence of metabolic activation, neither spironolactone nor potassium canrenoate has been shown to be mutagenic in mammalian tests *in vitro.* In the presence of metabolic activation, spironolactone has been reported to be negative in some mammalian mutagenicity tests *in vitro* and inconclusive (but slightly positive) for mutagenicity in other mammalian tests *in vitro.* In the presence of metabolic activation, potassium canrenoate has been reported to test positive for mutagenicity in some mammalian tests *in vitro,* inconclusive in others, and negative in still others.

In a three-litter reproduction study in which female rats received dietary doses of 15 and 50 mg/kg/day of spironolactone, there were no effects on mating and fertility, but there was a small increase in incidence of stillborn pups at 50 mg/kg/day. When injected into female rats (100 mg/kg/day for 7 days, i.p.), spironolactone was found to increase the length of the estrous cycle by prolonging diestrus during treatment and inducing constant diestrus during a 2-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), administered i.p. to female mice during a 2-week cohabitation period with untreated males, decreased the number of mated mice that conceived (effect shown to be caused by an inhibition of ovulation) and decreased the number of implanted embryos in those that became pregnant (effect shown to be caused by an inhibition of implantation), and at 200 mg/kg also increased the latency period to mating.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aldactone 25 mg contains: Calcium sulphate dehydrate, maize starch, polyvinyl pyrrolidone, magnesium stearate, peppermint flavor, hypromellose, polyethylene glycol and opaspray yellow (contains E171 and E172).

6.2 Incompatibilities

None stated.

6.3 Shelf-life

Refer to shelf-life statement on outer carton.

6.4 Special precautions for storage

Store in a dry place below 30°C.

6.5 Nature and contents of container

Aldactone 25 mg tablet is packed in PVC/foil blister packs containing 100 tablets.

6.6 Special precautions for disposal and other handling

None.

7. PRODUCT OWNER

Pfizer Inc.
New York
United States

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