Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aldactone 50 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of Spironolactone.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet (Tablets)
Round, white coloured, biconvex tablet with a peppermint odour embossed 'SEARLE over 916' on one side and the other side plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of refractory oedema associated with congestive cardiac failure; hepatic cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, diagnosis and treatment of primary aldosteronism, essential hypertension.

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

4.2 Posology and method of administration

Administration of Aldactone once daily with a meal is recommended.

Posology

Adults

Congestive heart failure: Usual dose - 100 mg/day. In difficult or severe cases the dosage may be gradually increased up to 200 mg/day. When oedema is controlled, the usual maintenance level is 75 mg/day to 200 mg/day.

Severe heart failure in conjunction with standard therapy (New York Heart Association Class III-IV): Based on the Randomized Aldactone Evaluation Study (RALES), treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg once daily in patients with a serum potassium ≤5.0 mEq/L and serum creatinine ≤2.5 mg/dL. Patients who tolerate 25 mg once daily may have their dose increased to 50 mg once daily as clinically indicated. Patients who do not tolerate 25 mg once daily may have their dose reduced to 25 mg every other day. See section 4.4 for advice on monitoring serum potassium and serum creatinine.

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

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

Nephrotic syndrome: Usual dose – 100 mg/day to 200 mg/day. Spironolactone has not been shown to be anti-inflammatory, nor to affect the basic pathological process. Its use is only advised if glucocorticoids by themselves are insufficiently effective.

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

Long test: Aldactone is administered at a daily dosage of 400 mg for 3 to 4 weeks. Correction of hypokalaemia and of hypertension provides presumptive evidence for the diagnosis of primary hyperaldosteronism.

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

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

Essential hypertension: Usual dose – 50 mg/day to 100 mg/day, which for difficult or severe cases may be gradually increased at 2 weekly intervals up to 200 mg/day. Treatment should be continued for 2 weeks or longer since an adequate response may not occur before this time. Dosage should subsequently be adjusted according to the response of the 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 in severe hepatic and renal impairment which may alter drug metabolism and excretion.

Paediatric population
Initial daily dosage should provide 1-3 mg of spironolactone per kilogram body weight, given in divided doses. Dosage should be adjusted on the basis of response and tolerance (see sections 4.3 and 4.4).

Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

4.3 Contraindications

Spironolactone is contraindicated in adult and paediatric patients with the following:

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

Spironolactone is contraindicated in paediatric patients with moderate to severe renal impairment.

Aldactone should not be administered concurrently with other potassium-conserving diuretics and potassium supplements should not be given routinely with Aldactone as hyperkalaemia may be induced.

4.4 Special warnings and precautions for use

Concomitant use of spironolactone with other potassium sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or other drugs or conditions known to cause hyperkalaemia, potassium supplements, a diet rich in potassium, or salt substitutes containing potassium, may lead to severe hyperkalaemia.

Hyperkalaemia may also occur in patients with impaired renal function. Cardiac dysrhythmias, occasionally fatal, may result.

The concomitant administration of this preparation with cardiac glycosides or hypotensive agents may necessitate adjustment of those drugs.

Reversible increases in blood urea may occur during use of the drug especially in the presence of impaired renal function.

Dilution hyponatraemia may occur in combination with other diuretics.

Patients who are being treated with this preparation require regular supervision with monitoring of fluid and electrolyte state. Periodic estimation of serum electrolytes is recommended due to the possibility of hyperkalaemia, 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.

The preparation should only be used with particular caution in elderly patients or those with potential obstruction of the urinary tract, or with disorders rendering their electrolyte balance precarious.

Spironolactone may induce gynaecomastia and menstrual irregularities.

Reversible hyperchloraemic metabolic acidosis, usually in association with hyperkalaemia, has been reported to occur in some patients with decompensated hepatic cirrhosis, even when renal function is normal.

Carcinogenicity: see section 5.3.

Hyperkalaemia in Patients with Severe Heart Failure
Hyperkalaemia may be fatal. It is critical to monitor and manage serum potassium in patients with severe heart failure receiving spironolactone. Avoid using other potassium-sparing diuretics. Avoid using oral potassium supplements in patients with serum potassium >3.5 mEq/L. The recommended monitoring for potassium and creatinine is 1 week after initiation or increase in dose of spironolactone, monthly for the first 3 months, then quarterly for a year, and then every 6 months. Discontinue or interrupt treatment for serum potassium >5 mEq/L or for serum creatinine >4 mg/dL (see section 4.2).

Paediatric population
Potassium-sparing diuretics should be used with caution in hypertensive paediatric patients with mild renal insufficiency because of the risk of hyperkalaemia. (Spironolactone is contraindicated for use in paediatric patients with moderate or severe renal impairment; see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of drugs known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia. In addition, concomitant use of trimethoprim/sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

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.

Concurrent use with carbenoxolone should be avoided.

Lithium
Spironolactone reduces the renal clearance of lithium, thus increasing the risk of lithium toxicity. Monitor lithium levels periodically when spironolactone is coadministered.

Hyperkalaemic metabolic acidosis has been reported in patients given spironolactone concurrently with ammonium chloride or colestyramine.

Potentiation of the effect of other diuretics and antihypertensive drugs occurs and their dosage may need to be reduced by about 50% when Aldactone is added to the treatment regime, and then adjusted as necessary. Concomitant administration with cardiac glycosides may necessitate adjustment of the dosages of these drugs.

Since ACE inhibitors decrease aldosterone production they should not routinely be used with Aldactone, particularly in patients with marked renal impairment.

Non-steroidal anti-inflammatory drugs such as aspirin, indomethacin and mefenamic acid may attenuate the natriuretic efficacy of diuretics due to the inhibition of intra-renal synthesis of prostaglandins and have been shown to attenuate the diuretic effect of spironolactone.

Spironolactone reduces vascular responsiveness to noradrenaline.

Caution should be exercised in the management of patients subjected to regional or general anaesthesia while they are being treated with Aldactone.

Spironolactone has been shown to increase the half-life of digoxin.

Spironolactone can interfere with assays for plasma digoxin concentrations.

Spironolactone enhances the metabolism of antipyrine.

In fluorimetric assays, spironolactone may interfere with the estimation of compounds with similar fluorescence characteristics.

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.

Spironolactone may reduce mitotane plasma levels in adrenocortical carcinoma patients treated with mitotane and should not be used concomitantly with mitotane.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of spironolactone in pregnant women. Studies in animals have shown reproductive toxicity associated with the anti-androgenic effect of spironolactone (see Section 5.3).

Diuretics can lead to reduced perfusion of the placenta and thus to impairment of intrauterine growth and are therefore not recommended for the standard therapy for hypertension and oedema during pregnancy.

Spironolactone should not be used during pregnancy, unless the potential benefit justifies the potential risks.

Breast-feeding

Canrenone (a major and active) metabolite of spironolactone, is excreted in human milk. There is insufficient information on the effects of spironolactone in newborns/infants.

Spironolactone should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from spironolactone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Spironolactone administered to female mice reduced fertility (see Section 5.3).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

The following adverse events have been reported in association with spironolactone therapy:
The following undesirable effects have been observed in clinical trials and reported during treatment with spironolactone with the following frequencies: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very Rare < 1/10,000	Frequency Not Known (cannot be estimated from the available data)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Benign breast neoplasm (male)			
Blood and lymphatic system disorders						Agranulocytosis, Leukopenia, Thrombocytopenia, Anaemia, Purpura, Eosinophilia
Metabolism and nutrition disorders	Hyperkalaemia		Electrolyte imbalance			
Psychiatric disorders		Confusional state				Libido disorder
Nervous system disorders		Dizziness				Headache, Drowsiness, Ataxia, Lethargy
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, Drug reaction with eosinophilia and systemic symptoms (DRESS), Alopecia, Hypertrichosis, Pemphigoid
Musculoskeletal and connective tissue disorders		Muscle spasms				
Renal and urinary disorders		Acute kidney injury				
Reproductive system and breast disorders		Gynaecomastia*, Breast pain**	Menstrual disorder			Impotence
General disorders and administration site conditions		Malaise				Drug fever

* Gynaecomastia may develop in association with the use of spironolactone. Development appears to be related to both dosage level and duration of therapy and is normally reversible when spironolactone is discontinued. In rare instances some breast enlargement may persist.
** In clinical trials, breast pain was reported more commonly in males than in females

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: potassium-sparing agents, ATC code C03DA01

Mechanism of action
Aldactone, as a competitive aldosterone antagonist, increases sodium excretion whilst reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action, maximum response being usually attained after 2-3 days treatment. Combination of Aldactone with a conventional, more proximally acting diuretic usually enhances diuresis without excessive potassium loss.

Severe Heart Failure
RALES was a multinational, double-blind study in 1663 patients with an ejection fraction of ≤35%, a history of NYHA Class IV heart failure within 6 months, and Class III-IV heart failure at the time of randomization. All patients were required to be taking a loop diuretic and, if tolerated, an ACE inhibitor. Patients with a baseline serum creatinine of >2.5 mg/dL or a recent increase of 25% or with a baseline serum potassium of >5.0 mEq/L were excluded. Patients were randomized 1:1 to spironolactone 25 mg orally once daily or matching placebo. Patients who tolerated 25 mg once daily had their dose increased to 50 mg once daily as clinically indicated. Patients who did not tolerate 25 mg once daily had their dosage reduced to 25 mg every other day. The primary endpoint for RALES was time to all-cause mortality. RALES was terminated early, after a mean follow-up of 24 months, because of significant mortality benefit detected on a planned interim analysis. Spironolactone reduced the risk of death by 30% compared to placebo (p<0.001- 95% confidence interval 18% - 40%). Spironolactone reduced the risk of cardiac death, primarily sudden death and death from progressive heart failure by 31% compared to placebo (p<0.001- 95% confidence interval 18% - 42%).

Spironolactone also reduced the risk of hospitalization for cardiac causes (defined as worsening heart failure, angina, ventricular arrhythmias or myocardial infarction) by 30% (p<0.001- 95% confidence interval 18% - 41%). Changes in NYHA class were more favorable with spironolactone: in the spironolactone group, NYHA class at the end of the study improved in 41% of patients and worsened in 38% compared to improved in 33% and worsened in 48% in the placebo group (p <0.001).

Paediatric population
There is a lack of substantive information from clinical studies on spironolactone in children. This is a result of several factors: the few trials that have been performed in the paediatric population, the use of spironolactone in combination with other agents, the small numbers of patients evaluated in each trial and the different indications studied. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in the scientific literature.

5.2 Pharmacokinetic properties

Spironolactone is well absorbed orally and is principally metabolised to active metabolites: sulfur containing metabolites (80%) and partly canrenone (20%).

Although the plasma half-life of spironolactone itself is short (1.3 hours) the half-lives of active metabolites are longer (ranging from 2.8 to 11.2 hours).

Paediatric population
There are no pharmacokinetic data available in respect of use in paediatric population. The dosage recommendations for paediatrics are based upon clinical experience and case studies documented in the scientific literature.

5.3 Preclinical safety data

Spironolactone has been shown to be tumourigenic in rats when administered at high doses over a long period of time. The significance of these findings with respect to clinical use is not known.
Nonclinical data reveal no evidence of teratogenicity, but embryo-fetal toxicity has been seen in rabbits, and an anti-androgenic effect in rat offspring has raised concern about possible adverse effects on male genital development. In rats, spironolactone was found to increase the length of the estrous cycle and in mice spironolactone inhibited ovulation and implantation, thereby decreasing fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Sulfate Dihydrate
Maize Starch
Povidone
Magnesium Stearate
Felcofix peppermint No.16433
Hypromellose
Macrogol 400
Opaspray White M-1-7111B (Contains Hypromellose and Titanium Dioxide (E171))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30 . Keep blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

The following presentations are registered:
PVC/foil blister packs of 50, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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