Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Spironolactone 50 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Spironolactone 50 mg film-coated tablets contain 50 mg spironolactone
Excipients with known effect: Lactose
Each tablet contains 150 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Spironolactone 50 mg film-coated tablets are white to pale white, round, biconvex tablets printed with "AE" on one side and no imprint on the other side.
50mg tablet diameter is approximately 10.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

· Oedema associated with congestive heart failure
· Severe heart failure, (NYHA III-IV)
· As an adjuvant in treatment of resistant hypertension
· Nephrotic syndrome
· Liver cirrhosis with ascites and oedema
· Diagnosis and treatment of primary hyperaldosteronism (Conn's syndrome)

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

Posology

Adults
The dosage should be determined individually depending on the condition and the degree of diuresis required. Dosage up to100 mg daily may be administered as a single dose or in divided doses.

Oedema associated with congestive heart failure
For management of oedema an initial daily dose of 100 mg of spironolactone administered in either single or divided doses is recommended, but may range from 25 to 200 mg daily. Maintenance dose should be individually determined.

Severe heart failure (NYHA Class III-IV)
Treatment in conjunction with standard therapy should be initiated at a dose of spironolactone 25 mg once daily if serum potassium is ≤ 5.0 mEq/L and serum creatinine is ≤ 2.5 mg/dL (221 µmol/L). 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.

Resistent Hypertension
The starting dose for spironolactone should be 25mg daily in a single dose; the lowest effective dose should be found, very gradually titrating upwards to a dose of 100mg daily or more.

Nephrotic syndrome
Usual dose is 100-200mg/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.

Hepatic cirrhosis with ascites and oedema
The starting dose is 100-200 mg per day, e.g. based on Na+/K+ ratio. If the response to 200 mg spironolactone within the first two weeks is not sufficient, furosemide is added and if necessary, the spironolactone dose is increased stepwise up to 400 mg per day. Maintenance dosage should be individually determined.

Diagnosis and treatment of primary aldosteronism
If primary hyperaldosteronism is suspected, spironolactone is given at a dose of 100 – 150 mg**,** or up to 400 mg daily. In the event of rapid onset of a strong diuretic and antihypertensive effect, this is a clear indication of elevated aldosterone production. In this case, 100 – 150 mg daily is administered for 3 – 5 weeks prior to surgery. If surgery is not an option, this dose is often sufficient to maintain blood pressure and potassium concentration at normal levels. In exceptional cases, higher doses are necessary, but the lowest possible dosage should be found.

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). The tablet may be ground or crushed and then suspended in water to make it easier to take.
Children should only be treated under guidance of a paediatric specialist. There is limited paediatric data available (see sections 5.1 and 5.2).

TheElderly
It is recommended that treatment is started at the lowest possible dose, then titrated with higher doses until the optimum effect is achieved. Caution is required, in particular in renal dysfunction.

Method of administration

The tablets should be taken with meals. Daily dosages in excess of 100 mg should be given in several divided doses.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Severe renal insufficiency (eGFR <30 mL per minute per 1.73 m^2), acute or progressive kidney disease (whether or not this is accompanied by anuria)
- Hyponatraemia
- Addison's disease
- Hyperkalaemia (serum potassium level > 5.0 mmol/L) at initiation
- Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements, or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB)

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

4.4 Special warnings and precautions for use

Monitoring fluid and electrolyte state

Spironolactone treatment may lead to hyperkalaemia, hyponatremia, and possible transient blood urea nitrogen (BUN) elevation. Patients who are being treated with spironolactone require regular supervision with monitoring of fluid and electrolyte state, especially in the elderly and/or in patients with pre-existing impaired renal or hepatic function.

The risk of hyperkalaemia, increases with decreasing renal function. Administration of spironolactone is contra-indicated in patients with hyperkalaemia and in patients with severe renal insufficiency (See Section 4.3) During treatment with spironolactone, severe hyperkalaemia can occur, which may result in cardiac arrest (sometimes fatal) in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements.

Hyperkalaemia may be accompanied by paraesthesia, weakness, mild paralysis or muscle spasms and is difficult to distinguish clinically from hypokalaemia. ECG changes may be the first sign of disturbed potassium balance, although hyperkalaemia is not always accompanied by an abnormal ECG.

Concomitant use of spironolactone with other potassium-sparing diuretics such as triamterene and amiloride) 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. See section 4.3 for contraindications.

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

Dilution hyponatraemia may occur in combination with other diuretics.

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

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.

Severe hepatic insufficiency
Caution is required in patients with hepatic disorders due to the risk of hepatic coma.

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. 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. Treatment should be discontinued or interrupted with serum potassium >5 mEq/L or with serum creatinine >4 mg/dL (see section 4.2).

Carcinogenicity
Animal studies have shown that at high doses and after long-term use, spironolactone induces tumours. The significance of these data for clinical application is unclear. However, the benefits of therapy should be weighed against the possible long-term harm before initiating long-term use of spironolactone in young patients.

Excipients
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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).

Concomitant use of medicinal products known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions affecting spironolactone

Combinations causing hyperkalaemia
Concomitant use of potassium-sparing diuretics (including eplerenone) or potassium-supplements , or dual-RAAS blockade with the combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) is contraindicated because of the risk of hyperkalaemia (see Section 4.3).

The use of ACE inhibitors in combination with spironolactone may be accompanied by hyperkalaemia, especially in patients with impaired renal function. Concomitant use requires careful dosing and close monitoring of the electrolyte balance.

Spironolactone and ciclosporin coadministration not recommended, as both increase serum potassium level and possible serious life-threatening interactions.

In addition, concomitant use of trimethoprim / sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

Heparin, low molecular weight heparin:
Concomitant use of spironolactone with heparin or low molecular weight heparin may lead to severe hyperkalemia. Increased diuresis has been observed during concomitant use of spironolactone and heparin.

Non-Steroidal Anti-Inflammatory Drugs
Acetyl salicylic acid, 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.

Interactions affecting other medicinal products

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

Anti-coagulants
Spironolactone reduces the effect of anticoagulants.

Anti-hypertensives
Spironolactone can potentiate the effect of antihypertensive agents. The dosage of such drugs, in particular ganglion-blocking drugs, can often be halved when spironolactone is added to the therapy. Concomitant administration with cardiac glycosides may necessitate adjustment of the dosages of these drugs.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Concurrent use with lithium salts should be avoided.

Carbenoxolone
As carbenoxolone may cause sodium retention and thus decrease the effectiveness of spironolactone, concurrent use should be avoided.

Digoxin
Spironolactone has been shown to increase the half-life of digoxin. This may result in increased serum digoxin levels and subsequent digitalis toxicity. 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.

Alcohol, barbiturates or narcotics
Potentiation of orthostatic hypotension may occur.

Cholestyramine
Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spironolactone concurrently with cholestyramine.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia, may occur.

Other forms of interaction

Ammonium Chloride
Hyperchloremic metabolic acidosis, frequently associated with hyperkalemia, has been reported in patients given spironolactone concurrently with ammonium chloride (e.g. in liquorice).

Plasma Cortisone levels
Spironolactone interferes with Mattingly's fluorimetric method for determination of plasma cortisone levels.

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.

Noradrenaline
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 spironolactone.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are very limited data on the use of spironolactone during pregnancy in humans.
Experimental animal studies have shown reproductive toxicity associated with the anti-androgenic effect of spironolactone (see section 5.3). Spironolactone should not be used during pregnancy unless the clinical condition of the woman requires treatment with spironolactone .
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 edema during pregnancy.

Breastfeeding
Canrenone, the principal and active metabolite of spironolactone, appears in small quantities in human breast milk. There is insufficient information on the effects of spironolactone in newborns/infants. 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 women.

Fertility
Spironolactone may induce impotence and menstrual irregularities (see section 4.8). Studies in animals suggest spironolactone may impair fertility (see Section 5.3).

4.7 Effects on ability to drive and use machines

No data are available on the ability to drive. Undesirable effects such as dizziness, confusion and headache may occur. The possible occurrence of these undesirable effects should be taken into account when driving or using machines.

4.8 Undesirable effects

The undesirable effects are dependent on dose and duration of treatment.
The most common adverse effects are hyperkalaemia (9%), disorders of the reproductive system and breasts, including gynaecomastia, reported in 13% of patients (at a dose of less than 100 mg). Gynaecomastia appears to be related to both dosage level and duration of therapy and is usually reversible once treatment stops. Other very common undesirable effects include headache, digestive system disorders, diarrhoea, fatigue and drowsiness.

The undesirable effects below are classified in accordance with the following frequencies: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1,000, <1/100), Rare (≥ 1/10,000, <1/1,000), Very rare (< 1/10,000), not known (cannot be estimated from the available data)

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Benign breast neoplasm (male),

Blood and lymphatic system disorders
Rare: thrombocytopenia, eosinophilia, leukopenia (including agranulocytosis), anaemia, purpura

Metabolism and nutrition disorders

Very common: hyperkalaemia
Uncommon: Electrolyte imbalance

Psychiatric disorders
Common: confusional state
Not known: Libido disorder

Nervous system disorders
Common: dizziness
Not known: headache, ataxia, lethargy, drowsiness

Gastrointestinal disorders
Common: nausea
Not known: gastrointestinal disorder

Hepatobiliary disorders
Uncommon: hepatic function abnormal

Skin and subcutaneous tissue disorders
Common: pruritus, rash
Uncommon: urticaria
Not known: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), alopecia, hypertrichosis, pemphigoid

Musculoskeletal and connective tissue disorders
Common: muscle spasms

Renal and urinary disorders
Common: elevated serum creatinine levels, acute renal failure

Reproductive system and breast disorders
Common: gynaecomastia*, breast pain**
* 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.

Uncommon: menstrual disorder
Not known: impotence

General disorders and administration site conditions
Common: malaise
Not known: Drug fever

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

Overdose can manifest itself in the form of nausea and vomiting, and (more rarely) by drowsiness, mental confusion, dizziness, maculopapular or erythematous rash or diarrhoea. Dehydration may occur.
In addition, infertility can occur at very high doses (450 mg/day).
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 disturbances. No specific antidote has been identified. Improvement may be expected after withdrawal of the drug.

If electrolyte balance disturbance and dehydration occur,treatment is symptomatic and supportive and may include 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: cardiovascular system, diuretics, potassium-sparing diuretics, aldosterone antagonist.

ATC code: C03DA01

Mechanism of action
Spironolactone, 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 to 3 days treatment. Combination of spironolactone with a conventional, more proximally acting diuretic usually enhances diuresis without excessive potassium loss.

Severe heart failure:RALES
The Randomized Aldactone Evaluation Study (RALES) was a multinational, double-blind study in 1663 patients with an ejection fraction of ≤ 35%, a history of New York Heart Association (NYHA) class IV heart failure within 6 months, and class III-IV heart failure at the time of randomisation. All patients were taking a loop diuretic, 97% were taking an ACE inhibitor and 78% were on digoxin (at the time this trial was conducted, beta-blockers were not widely used to treat heart failure and only 15% were treated with a beta-blocker). 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 a significant mortality benefit detected on a planned interim analysis. Spironolactone reduced the risk of death compared to placebo (mortality spironolactone 284/841 (35%); placebo 386/822 (46%); Risk reduction 30%; 95% confidence interval 18% to 40%; p<0.001). Spironolactone also significantly 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%). In the spironolactone group, NYHA class at the end of the study improved in 41% of patients and worsened in 38% compared to an improvement in 33% and a worsening in 48% of the patients 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 scientific literature.

5.2 Pharmacokinetic properties

Absorption
Approximately 70% of spironolactone is absorbed after oral administration. The bioavailability of spironolactone can be increased if it is taken with food. The clinical relevance of this effect is however not entirely clear. Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (tmax), peak plasma concentration (Cmax), and elimination half-life (t1/2) for spironolactone is 2.6 hr., 80ng/ml, and approximately 1.4hr., respectively. For the 7-alpha- (thiomethyl) spironolactone and canrenone metabolites, tmax was 3.2 hr. and 4.3 hr., Cmax was 391 ng/ml and 181 ng/ml, and t1/2 was 13.8 hr. and 16.5 hr, respectively.

Distribution
Both spironolactone and canrenone are over 90% bound to plasma proteins.

Biotransformation
Spironolactone is extensively metabolised to active metabolites: including thiomethyl- spironolactone and canrenone.

Elimination
The plasma half-life of spironolactone is approximately 1.5 hours, that of 7a-thiomethyl- spironolactone approximately 9-12 hours and that of canrenone 10-35 hours. Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces. The renal action of a single dose of spironolactone reaches its peak after 7 hours, and activity persists for at least 24 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. Endocrine disrupting effects have also been observed in female rodents at clinically relevant exposures. In adult rats, spironolactone was found to increase the length of the estrous cycle, and in female offspring exposed late in pregnancy, endocrine dysfunction persisting to adulthood was observed. In mice spironolactone inhibited ovulation and implantation, thereby decreasing fertility. The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Pregelatinised corn starch
Calcium hydrogen phosphate, anhydrous
Povidone K25
Peppermint oil
Purified talc
Silica, colloidal anhydrous
Magnesium stearate (E470b)

Film coating:
Hypromellose
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister pack: 3 years
Bottles: 24 months
in-use shelf-life after first opening: 3 months.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Tablets are packed in PVC-Aluminium blister pack & HDPE bottle pack

Pack sizes:
Blister pack: 20, 28, 30, 50, 60, 90 and 100 tablets in blister.
HDPE bottle: 250, 500 and 1000 tablets (for hospital or dose dispensing use only)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/119/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 29th January 2016
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10 DATE OF REVISION OF THE TEXT

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