SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Spironolactone 100mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Spironolactone 100 mg film-coated tablets contain 100 mg spironolactone
Excipients with known effect: Lactose
Each tablet contains 300 mg lactose monohydrate.

For the full list of excipients,
see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Spironolactone 100 mg film-coated tablets are white to pale white, round, biconvex tablets printed with “AF” on one side and no imprint on the other side.
100mg tablet diameter is approximately 11.2 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 $\leq$ 5.0 mEq/L and serum creatinine is $\leq$ 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).

The Elderly
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
- 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

Fluid and electrolyte balance
During long-term therapy with spironolactone, fluid and and electrolyte status should be regularly monitored, especially in elderly patients. Administration of spironolactone is not recommended if plasma potassium levels are elevated and contra-indicated in 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.

Combination with potent potassium-sparing diuretics such as triamterene and

amiloride is contra-indicated in order to prevent hyperkalaemia and care should be taken to avoid administration of extra potassium

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

Impaired renal function
Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria. The risk of hyperkalaemia increases with decreasing renal function. Therefore, these patients should be treated with caution.

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

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.

Lactose
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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).

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 recomended, as both increase serum potassium level and possible serious life-threatening interactions.

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 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.

Noradrenalin
Spironolactone reduces the vasoconstrictive effects of noradrenaline.

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.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

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

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.

In addition to other medicinal products known to cause hyperkalaemia concomitant use of trimethoprim / sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

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

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.
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. 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 women.

Fertility
Spironolactone may induce impotence and menstrual irregularities (see section 4.8).

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)
Very rare: breast cancer

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

Immune system disorders
Rare: eczema (type 1 allergic reaction), hypersensitivity

Endocrine disorders
Not known: slight androgenic effects, including hirsutism.

Metabolism and nutrition disorders
Very common: hyperkalaemia in patients with severe renal dysfunction who are receiving concomitant treatment with potassium supplements (see also section 4.4)
Common: hyponatraemia (in particular during combined intensive therapy with thiazide diuretics), hyperkalaemia in (1) patients with severe renal dysfunction, (2) patients receiving treatment with ACE inhibitors or potassium chloride, (3) the elderly, and (4) diabetic patients
Uncommon: acidity of the blood (acidosis) in patients with liver problems
Rare: insufficient fluid in the tissues (dehydration), porphyria, temporary increase in nitrogen levels in the blood and urine, hyperuricemia (may lead to gout in predisposed patients)
Not known: reversible hyperchloraemic metabolic acidosis – usually accompanied by hyperkalaemia has been reported in some patients with decompensated hepatic cirrhosis, even where renal function was normal.

Psychiatric disorders
Uncommon: confusion

Nervous system disorders
Very common: headache
Common: weakness, lethargy in patients with cirrhosis, tingling (paraesthesia)
Rare: paralysis, paraplegia of the limbs due to hyperkalaemia
Not known: dizziness, ataxia

Vascular disorders
Very rare: inflammation of the vessel walls (vasculitis)
Not known: mild hypotension

Gastrointestinal disorders

Very common: indigestion, diarrhoea
Common: nausea and vomiting
Very rare: gastric inflammation, gastric ulcers, intestinal haemorrhage, cramps

Hepatobiliary disorders
Very rare: hepatitis

Skin and subcutaneous tissue disorders
Uncommon: skin rash, urticaria, erythema, chloasma, pruritus, exanthema
Very rare: alopecia, eczema, erythema annulare centrifugum (EAC), hypertrichosis
Not known: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), Pemihigoid

Musculoskeletal and connective tissue disorders
Uncommon: muscle spasms, leg cramps
Very rare: systemic lupus erythematosus (SLE), Osteomalacia

Renal and urinary disorders
Uncommon: elevated serum creatinine levels
Very rare: acute renal failure

Reproductive system and breast disorders
Very common: Men: reduced libido, erectile dysfunction, impotence, enlargement of the mammary glands (gynaecomastia);
Women: breast disorders, tenderness of the breasts, menstrual disorders, deepening of the voice (in many cases irreversible)
Common: Women: changes in vaginal secretions, reduced libido, absence of periods (amenorrhoea), post-menopausal bleeding

General disorders and administration site conditions
Very common: fatigue, drowsiness
common: malaise

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Overdose can manifest itself in the form of nausea and vomiting, and (more rarely) by drowsiness, confusion, skin rash or diarrhoea.

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

Spironolactone affects the kidney and the adrenal gland (as an antagonist of aldosterone in the renal tubuli and an inhibitor of aldosterone synthesis in high concentrations).
Spironolactone promotes diuresis in patients with oedema or ascites by increasing excretion of sodium
in the urine. Potassium loss caused by thiazide diuretics is reduced. It has a gradual and prolonged action.
The antihypertensive effect of spironolactone is based on water and salt depletion.

Severe heart failure: RALES
The Randomized Aldactone Evaluation Study (RALES) was a multinational, double-blind study in 1663 patients with an ejection fraction of $\leq$ 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 as well as the risk of hospitalization for

cardiac causes.

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 7 - 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

Preclinical data do not add relevant information to that already mentioned in

other sections of this SmPC.

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.

Studies on reproduction toxicity have not shown an increased risk of congenital anomalies, but an anti-androgenic effect in rat offspring has raised concern about possible adverse effects on male genital development. There is no confirmation in humans of these possible adverse effects.

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)

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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0458

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