SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Spironolactone 100mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg of spironolactone.

Spironolactone 100mg Tablets contain 48 mg of lactose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Buff coloured biconvex film coated tablet marked 100 on one side and BL on the reverse

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Spironolactone is indicated in

1) Hepatic cirrhosis with ascites and oedema

2) Malignant ascites

3) Nephrotic syndrome

4) Diagnosis and treatment of primary aldosteronism

5) Congestive heart failure

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

Spironolactone Tablets should always be administered with fluid and preferably with food to aid absorption.

Adults:

Hepatic cirrhosis with ascites and oedema:

If urinary Na^+/K^+ ratio is greater than 1.0, 100mg/day. If the ratio is less than 1.0, 200mg/day to 400mg/day. Maintenance dosage should be individually determined.

Malignant ascites

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

Nephrotic syndrome

Usually dose 100mg/day to 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.

Congestive heart failure with oedema

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 mg to 200 mg daily. Maintenance dose should be individually determined.

Severe heart failure (New York Heart Association Class III-IV)
Based on the Randomized Aldactone Evaluation Study (RALES: see also section 5.1), 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. 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.

Diagnosis and treatment of primary aldosteronism

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

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

Short test - Spironolactone is administered at a daily dosage of 400mg 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.

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

Elderly
It is recommended that treatment should be 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 1-3mg of spironolactone per kg bodyweight given in divided doses. Dosage should be adjusted on the basis of response and tolerance (see sections 4.3 and 4.4). If necessary the tablets may be crushed and taken dispersed in food or drink.

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

Method of Administration

For oral administration.
Administration of Spironolactone tablets once daily with a meal is recommended.

4.3 Contraindications

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

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Acute renal insufficiency, significant renal compromise, anuria.
- Hyperkalaemia
- Addison's disease.
- Concomitant use of eplerenone or other potassium sparing diuretics.

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

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

4.4 Special warnings and precautions for use

Fluid and electrolyte balance

Fluid and electrolyte status be regularly monitored particularly in the elderly and in those with significant renal and hepatic impairment.

Hyperkalaemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Should hyperkalaemia develop, Spironolactone should be discontinued, and if necessary, active measures taken to reduce the serum potassium to normal (section 4.3).

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

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.

Urea

Reversible increases in blood urea have been reported in association with Spironolactone therapy, particularly in the presence of impaired renal function.

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).

Caution is required in severely ill patients and those with relatively small urine volumes who are at greater risk of developing hyperkalaemia.

Caution is required in patients with a predisposition to metabolic or respiratory acidosis. Acidosis potentiates the hyperkalaemic effects of spironolactone and spironolactone may potentiate acidosis.

Spironolactone has been shown to produce tumours 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 certain. However, the long-term use of spironolactone in young patients requires careful consideration of the benefits and the potential hazard involved.

Caution should be exercised in patients diagnosed with porphyria as Spironolactone is considered unsafe in these patients.

Care should be taken in patients suffering from menstrual abnormalities or breast enlargement.

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).

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking Spironolactone. Pulmonary oedema typically develops within minutes to hours after Spironolactone intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Spironolactone should be withdrawn and appropriate treatment given. Spironolactone should not be administered to patients who previously experienced ARDS following Spironolactone intake.

Important information regarding the ingredients of spironolactone tablet

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

Sodium - This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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.

ACE inhibitors – since ACE inhibitors decrease aldosterone production and they should not routinely be used with spironolactone, particularly in patients with marked renal impairment. Concomitant use of Spironolactone with ACE-inhibitors may lead to severe hyperkalaemia, particularly in patients with renal failure. Spironolactone may also have an enhanced hypotensive effect when administered concomitantly with ACE-inhibitors.

Angiotensin-II receptor antagonists - concurrent administration of angiotensin-II receptor antagonists, e.g. valsartan, losartan, and spironolactone may result in an increase in serum potassium levels. If concurrent use is necessary, monitor serum potassium levels.

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

Anti-hypertensive agents - Potentiation of the effect of antihypertensive drugs occurs and their dosage may need to be reduced when Spironolactone is added to the treatment regime and then adjusted as necessary. Since ACE inhibitors decrease aldosterone production they should not routinely be used with spironolactone, particularly in patients with marked renal impairment.

Anti-diabetics - Administration with chlorpropamide may increase risk of hyponatraemia.

Aspirin may reduce the diuretic effect of Spironolactone

Ciclosporin – Co-administration of potassium sparing diuretics with ciclosporin may result in hyperkalaemia. Avoid concurrent use of spironolactone and ciclosporin. If concurrent therapy is necessary, monitor serum potassium levels for persistent elevations in patients.

Potassium salts- potassium supplements are contraindicated except in cases of initial potassium depletion. If potassium supplementation is considered essential, serum electrolytes should be monitored.

Ulcer-healing drugs - as carbenoxolone may cause sodium retention and thus decrease the effectiveness of Spironolactone, concurrent use should be avoided.

Non-steroidal anti-inflammatory drugs 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 attenuate the diuretic effect of spironolactone. There may be an increased risk of nephrotoxicity and hyperkalaemia when NSAIDs, notably/particularly Indometacin are used with Spironolactone. Indometacin and mefenamic acid inhibit the excretion of canrenone reducing the diuretic effect. Spironolactone enhances the metabolism of antipyrine.

Sympathomimetics - 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.

Corticosteroids - co-administration of Spironolactone with fludrocortisone may result in a paradoxical dose- related increase in urinary potassium excretion. If concomitant administration is necessary, closely monitor serum potassium levels.

Diuretics - Spironolactone should not be administered concurrently with other potassium-conserving diuretics as this may induce hyperkalaemia. Potassium canrenoate, a metabolite of Spironolactone, has been shown to cause myeloid leukaemia in rats.

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

Lithium - concurrent use of lithium and Spironolactone may result in increased lithium concentrations and lithium toxicity (weakness, tremor, excessive thirst and confusion) due to decreased lithium excretion. If concomitant therapy is necessary, monitor serum lithium levels

within the first 5-7 days of adding or discontinuing Spironolactone and periodically thereafter. Lower lithium doses may be required with concomitant Spironolactone therapy.

Tacrolimus - Spironolactone should not be used in patients receiving tacrolimus due to risk of mild to severe hyperkalaemia.

Liver function tests - Spironolactone may enhance the metabolism of antipyrine used in liver functions tests.

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

Colestyramine - reports of hyperchloraemic metabolic acidosis

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

Spironolactone or its metabolites may cross the placental barrier. The use of Spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the mother and foetus.

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 risk.

Breast-feeding

Canrenone (a major and active) metabolites of spironolactone have been detected in breast milk. If use of spironolactone is considered essential, an alternative method of infant feeding should be instituted.

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
Feminisation has been observed in male rat foetuses with spironolactone therapy. 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

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 the drug is discontinued. In rare instances some breast enlargement may persist.

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

System Organ Class	Very common (≥1/10)	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10000 to <1/1000	Very Rare <1/10000	Frequenc known (estimatec available
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Benign breast neoplasms (male)			

Blood and lymphatic system disorders				Elevation in blood urea nitrogen (BUN)		Leukoper (Agranul Eosinoph Thrombo
Metabolism and nutrition disorders	Hyperkalaemia		Electrolyte imbalance	Hyponatraemia, Hyperkalaemia		
Psychiatric disorders		Confusional state				Lethargy disorder
Nervous system disorders:		Dizziness	Ataxia, drowsiness, headache, clumsiness			
Respiratory, thoracic and mediastinal disorder					Acute respiratory distress syndrome (ARDS) (see section 4.4)	
Gastrointestinal disorders		Nausea				Gastroint disorders Gastritis, bleeding, gastroint disturban stomach
Hepatobiliary disorders			Hepatic function abnormal			Hepatoto
Skin and subcutaneous tissue disorder		Pruritus, Rash	Urticaria			Toxic necrolysi Stevens-J syndrom reaction eosinoph systemic symptom (DRESS) Alopecia Hypertric Pemphig

Musculo-skeletal and Connective tissue disorders		Muscle spasms				Leg cram Osteoma
Renal and urinary disorders		Acute Kidney injury				
Reproductive system and breast disorders		Gynaecomastia, Breast pain (male)[a]	Menstrual disorder, Breast pain (female)[b]	Breast enlargement, Alteration in voice pitch, which may not be reversible, impotence and decreased sexual ability		
General disorders and administration site conditions		Malaise				

Abbreviations: CDS = Core Data Sheet; F = female; LLT = lower level term;

M = male; PT = preferred term; WHO-ART = World Health Organization Adverse Drug Reaction Terminology.

[a] The term Breast pain is mapped from CDS and the frequency is derived from WHO-ART term Breast pain (M); however, Breast pain male is the LLT.

[b] Breast pain is the PT from CDS, and the frequency is derived from WHO-ART term Breast pain (F).

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:

Acute overdosage may be manifested by drowsiness, mental confusion, nausea, vomiting, dizziness or diarrhoea. Hyperkalaemia or hyponatraemia may be induced but these effects are unlikely to be associated with acute overdosage.

Symptoms of hyperkalaemia may manifest as paraesthesia, muscular 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.

Treatment: No specific antidote has been identified. Improvement may be expected on 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

Spironolactone, as a competitive aldosterone antagonist, increasessodium excretion whilst reducing potassium loss at the distal renal tubule.

It has a gradual and prolonged action.

Clinical Efficacy and Safety

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 taking a loop diuretic, 97% were taking an ACE inhibitor and 78% were on digoxin (at the time this trial was conducted, b-blockers were not widely used to treat heart failure and only 15% were treated with a b-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 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 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. Changes in NYHA class were more favorable with spironolactone. Gynaecomastia or breast pain was reported in 10% of men who were treated with spironolactone, as compared with 1% of men in the placebo group ($p<0.001$). The incidence of serious hyperkalaemia was low in both groups of patients.

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

Absorption: Spironolactone is incompletely but fairly rapidly absorbed from the gastrointestinal tract and the extent of absorption will depend on the particle size and formulation and is improved after food. Bioavailability is estimated from 60 to 90%. Time to peak plasma concentration is approximately one hour.

Distribution: Although the plasma half-life of Spironolactone itself is short (1.3 hours) the half-lives of the active metabolites are longer (ranging from 2.8 to 11.2 hours). Spironolactone is estimated to be 90% protein bound. Volume of distribution, extent of tissue accumulation and ability to cross the blood brain barrier are not known. Spironolactone or its metabolites may cross the placental barrier and canrenone is secreted in breast milk. Spironolactone is known to have a slow onset of action (two to three days), and a slow diminishment of action.

Biotransformation: The main site of biotransformation is the liver where it is metabolised, to 80% sulphur containing metabolites such as 7 alpha-thiomethylspironolactone and canrenone (20%). Many of these metabolites also have a diuretic- activity. Canrenone, which is an active metabolite, has a biphasic plasma half-life of about 4-17 hours.

Elimination: Following the administration of 100 mg of spironolactone daily for 15 days in non-fasted healthy volunteers, time to peak plasma concentration (t_{max}), peak plasma

concentration (C_{max}), and elimination half-life ($t_{½}$) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 hr., respectively. For the 7-alpha-(thiomethyl) spironolactone and canrenone metabolites, t_{max} was 3.2 hr. and 4.3 hr., C_{max} was 391 ng/ml and 181 ng/ml, and $t_{½}$ was 13.8 hr. and 16.5 hr., respectively.

The renal action of a single dose of Spironolactone reaches its peak after 7 hours, and activity persists for at least 24-hours. Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

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

Carcinogenicity: Spironolactone has been shown to produce tumours 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 certain. However, the long-term use of spironolactone in young patients requires careful consideration of the benefits and potential hazards involved. Spironolactone or its metabolites may cross the placental barrier. With spironolactone, feminisation has been observed in male rat foetuses. The use of Spironolactone in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the mother and foetus.

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.

6.1 List of excipients

Tablet core:

Colloidal anhydrous silica

Sodium lauryl sulfate
Rice starch
Microcrystalline cellulose PH101

Agar
Lactose monohydrate
Peppermint oil
Povidone K-29-32

Magnesium stearate

Tablet coat:

Methyl hydroxypropyl cellulose
Polyethylene glycol 400
Opaspray M-1-6031B (E171, E464, E172)
Talc.

Colloidal anhydrous silica, sodium lauryl sulfate, rice starch, microcrystalline cellulose PH101, lactose monohydrate, peppermint oil, povidone K-29-32, industrial methylated spirit, magnesium stearate, methyl hydroxypropyl cellulose, polyethylene glycol 400, opaspray M-1-6031B (E171, E464, E172), and talc.

6.2 Incompatibilities

None stated.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Do not store above 25°C

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Securitainers with white bodies, blue lids, containing 21, 28, 100, 250, 500 or 1000 tablets*

PVC/PVdC//Al blister pack containing 28 tablets.

For bulk supply, only packs of 5, 000 and 10,000 tablets will be available (supplied in polybags, free from additives, inside a card board outer container).

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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