SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Spironolactone 25mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25mg of spironolactone.
Spironolactone 25mg Tablets contain 52.95mg of lactose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.

Buff coloured biconvex film coated tablet marked 25 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 (it is not an indication in the absence of these complications)
2) Malignant ascites
3) Nephrotic syndrome
4) Diagnosis and treatment of primary hyperaldosteronism
5) Congestive cardiac failure.

4.2 Posology and method of administration
For oral administration
Administration of Spironolactone Tablets once daily 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 ratio is less than 1.0, 200-400mg/day. Maintenance dosage should be individually determined.

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

*Nephrotic syndrome:* Usual dose 100-200mg/day. Spironolactone has not been shown to be anti-inflammatory, or to affect the basic pathological process. (its use only advised if glucocorticoids by themselves are insufficiently effective).

*Congestive heart failure:* Usual dose 100mg/day, may be increased up to 400mg/day in difficult or severe cases. The usual maintenance level, when oedema is controlled is 25-200mg/day.

*Diagnosis and treatment of primary aldosteronism:* Spironolactone Tablets 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/day for three to four weeks. Correction of hypokalaemia and of hypertension provides presumptive evidence for diagnosis of primary hyperaldosteronism.

*Short test* - Spironolactone is administered at a daily dosage of 400mg/day for four days. If serum potassium increases during spironolactone administration but falls 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 100-400mg/day in preparation for surgery.
For patients who are considered unsuitable for surgery, spironolactone may be used 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 increased as required to achieve maximum benefit. Care should be taken in severe hepatic and renal impairment which may alter drug metabolism and excretion. The elderly in general are more likely to be at risk of hyperkalaemia- monitor renal function more frequently in the elderly.

**Paediatric population**

Initial daily dosage - 3mg/kg/body weight in divided doses. Dosage should be adjusted on basis of response and tolerance. If necessary the tablets may be crushed and taken dispersed in food or drink.

### 4.3 Contraindications

Spironolactone is contraindicated in the following:

- Patients who are hypersensitive to spironolactone or to any of the excipients listed in section 6.1.
- Patients with anuria (patients are at greater risk of developing hyperkalaemia),
- acute renal insufficiency, severe or rapidly progressing impairment of renal function (spironolactone may aggravate electrolyte imbalance and the risk of developing hyperkalaemia is increased),
- hyperkalaemia (spironolactone may further increase serum potassium concentrations),
- Addison’s disease.
- Diabetes mellitus, especially in patients with confirmed or suspected renal insufficiency
- Diabetic nephropathy (increased risk of hyperkalaemia. Spironolactone should be discontinued at least 3 days prior to a glucose tolerance test because of the risk of severe hyperkalaemia)

Breast-feeding is contra-indicated

### 4.4 Special warnings and precautions for use
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 hazards involved.

Fluid and electrolyte status should be regularly monitored particularly in the elderly, 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. Dilutional hyponatraemia may be induced, particularly when Spironolactone is given in combination with other diuretics.

Care should be taken in patients suffering from hyponatraemia.

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.

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

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

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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 with spironolactone may result in an increase in serum potassium levels and may lead to severe hyperkalaemia. 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.

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.

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

Aspirin may reduce the diuretic effect of Spironolactone

Ciclosporin – coadministration 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.
Potassium salts - potassium supplements are not recommended except in cases of initial potassium depletion. If potassium supplementation is considered essential, serum electrolytes should be monitored.

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

Non-steroidal anti-inflammatory drugs may attenuate the natriuretic efficacy of diuretics, due to inhibition of intrarenal synthesis of prostaglandins. There may be an increased risk of nephrotoxicity and hyperkalaemia when NSAIDs, notably Indometacin are used with Spironolactone. Indomethacin and mefenamic acid inhibit the excretion of canrenone reducing the diuretic effect.

Sympathomimetics - Spironolactone reduces the vascular responsiveness to noradrenaline (norepinephrine). Caution should be exercised in 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.

Coumarins - in patients receiving oral anticoagulant therapy with warfarin, the prothrombin time ratio or INR (international normalised ratio) should be monitored with the addition and withdrawal of treatment with Spironolactone, and should be reassessed periodically during concurrent therapy. Adjustments of the warfarin dose may be necessary in order to maintain the desired level of anticoagulation.

Diuretics - Spironolactone should not be administered concurrently with other potassium-conserving diuretics as hyperkalaemia may be induced. 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 undergoing therapy with tacrolimus as concomitant use has resulted in mild to severe hyperkalaemia.

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

Cancer medication – avoidance of Spironolactone recommended if receiving Mitotane treatment.

Colestyramine- reports of hyperchloraemic metabolic acidosis

Oestrogen- diuretic effect of Spironolactone antagonised by oestrogen

4.6  **Fertility, pregnancy and lactation**
Spironolactone or its metabolites may cross the placental barrier. Use in pregnancy requires that the anticipated benefits be weighed against possible hazards to mother and foetus.

**Lactation**
Canrenone, a metabolite of spironolactone has been detected in breast milk. If use of Spironolactone is considered essential, an alternative method of infant feeding should be used.

**Fertility**
Feminism has been observed in male rat foetuses with spironolactone therapy.
4.7 Effects on ability to drive and use machines
Drowsiness and dizziness may occur, therefore, care should be taken when driving or operating machinery.

4.8 Undesirable effects
Reproductive system and breast disorders: 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. Alteration in voice pitch may also occur on rare occasions, which may not be reversible. Impotence and decreased sexual ability has been reported. This is usually reversible on discontinuation of Spironolactone. Mild androgenic effects like breast tenderness and increased hair growth in females, irregular menstrual periods and sweating have been reported.

Blood and lymphatic system disorders: leukopenia (including agranulocytosis), eosinophilia and thrombocytopenia have been reported rarely. Spironolactone may cause transient elevations in blood urea nitrogen (BUN) especially in patients with renal impairment. Hyponatraemia has been reported rarely.

Hypersensitivity: these occur rarely and are usually mild but very occasionally may be severe causing swelling, shock and collapse. Shortness of breath, skin rash or itching has been reported rarely.

Metabolic and nutritional disorders: electrolyte disturbances, hyponatraemia and hyperkalemia have been reported rarely.

Nervous system disorders: ataxia, drowsiness, dizziness, headache, mental confusion and clumsiness have been reported although these are less common.

Body as a whole: malaise, drug fever

Cardiac disorders: severe hyperkalaemia may result in paralysis, flaccid paraplegia and cardiac arrhythmias with subsequent cardiovascular collapse. This can be fatal in patients with impaired renal function.

Hepatobiliary disorders: hepatic function abnormal, hepatotoxicity has been reported
Gastrointestinal disorders: gastritis, gastric bleeding, gastrointestinal disturbances, stomach cramps, diarrhoea, vomiting and ulceration are more frequent events

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) have been reported. Alopecia, hypertrichosis, pruritus, rash and urticaria has been reported rarely.

Musculoskeletal disorders, connective tissue and bone disorders: leg cramps, osteomalacia

Psychiatric disorders: lethargy, changes in libido, confusion

Renal and urinary system disorder: acute renal failure, particularly in those with pre-existing renal impairment.

Neoplasms benign, malignant and unspecified (including cysts and polps): benign breast neoplasms

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

4.9 Overdose
Symptoms: - Acute overdose may be manifested by Drowsiness, mental confusion, nausea, vomiting, dizziness or diarrhoea. Hyperkalaemia or hyponatraemia may be induced but these are unlikely to be associated with acute overdosage. Symptoms of hyperkalaemia may manifest as paraesthesia, lassitude, 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: There is no specific antidote has been identified. Improvement may be expected on cessation of therapy.

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

ATC Code: C03D A01

Spironolactone is a steroid with a structure resembling that of the natural adrenocorticoid hormone, aldosterone. Spironolactone is a potassium-sparing diuretic. It is a competitive antagonist of the action of mineralocorticosteroids, of which the sodium retaining hormone aldosterone is the most potent naturally occurring compound.

Block of the action of aldosterone on the distal tubule results in an increase in the excretion of sodium and chloride, but potassium, hydrogen and ammonium excretion are decreased. The diuretic action is weak. Spironolactone is used when aldosterone is an important cause of fluid overload.

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.

Metabolism- The main sight 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- Spironolactone is excreted in the urine and faeces in the form of metabolites.

The renal action of a single dose of Spironolactone reaches its peak after 7 hours, and activity persists for at least 24-hours.

5.3 Preclinical safety data
Not relevant

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Colloidal anhydrous silica, sodium lauryl sulphate, rice starch, microcrystalline cellulose PH101, agar, 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), purified water 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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