SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Spironolactone 25mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Spironolactone 25mg

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet
Pale yellow, bi-convex tablets engraved with SPR25.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Administration of Spironolactone Tablets once daily with a meal is recommended.

Posology

Adults:

Hepatic cirrhosis with ascites and oedema

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

Malignant ascites

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

Nephrotic syndrome

Usual dose 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.

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 tests: Spironolactone tablets are administered at a daily dosage of 400mg for three to four weeks. Correction of hypokalaemia and of hypertension provides presumption evidence for the diagnosis of primary hyperaldosteronism.

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

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

Congestive cardiac failure with oedema

For management of oedema an initial daily dose of 100mg 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 (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.

Elderly
It is recommended that treatment is started with the lowest dose and titrated upwards as required to achieve maximum benefit. Care should be taken with severe hepatic and renal impairment which may alter drug metabolism and excretion.

Paediatric population
Initial daily dosage should provide 1-3mg of spironolactone per kilogram 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 a suspension may be prepared by crushing Spironolactone tablets. A suitable suspending vehicle is Methylcellulose 20% v/v, purified water to 100%. Such suspension is stable for one month when refrigerated.

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

4.3 Contraindications

Spironolactone tablets are contraindicated in adults and paediatric patients with the following:

- acute renal insufficiency, significant renal compromise, anuria.
- Addison's disease or other conditions associated with hyperkalaemia.
- hyperkalaemia
- hypersensitivity to spironolactone or to any of the excipients listed in section 6.1.
- concomitant use of eplerenone or other potassium sparing diuretics..

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

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

4.4 Special warnings and precautions for use

Fluid and electrolyte balance: Fluid and electrolyte status should be regularly monitored particularly in the elderly, in those with significant renal

and hepatic impairment. Patients with hepatic impairment should be carefully monitored as hepatic coma may be precipitated in susceptible patients.

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 (see 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 diurectics, angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs, angiotensin II antagonists, aldosterone blockers, heparin, low molecular weight heparin or other drugs 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 one 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 >5mEq/L or for serum creatinine >4 mg/dL (see section 4.2).

Paediatric population

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of drugs known to cause hyperkalaemia with spironolactone may result in severe hyperkalaemia. In addition, concomitant use of

trimethoprim/sulfamethoxazole (co-trimoxazole) with spironolactone may result in clinically relevant hyperkalaemia.

Spironolactone has been reported to increase serum digoxin concentration and to interfere with certain serum digoxin assays. In patients receiving digoxin and spironolactone the digoxin response should be monitored by means other than serum digoxin concentrations, unless the digoxin assay used has been proven not to be affected by spironolactone therapy. If it proves necessary to adjust the dose of digoxin patients should be carefully monitored for evidence of enhanced or reduced digoxin effect.

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.

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.

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.

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

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

Spironolactone enhances the metabolism of antipyrine.

Spironolactone can interfere with assays for plasma digoxin concentrations.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Spironolactone or its metabolites may cross the placental barrier. With spironolactone, feminisation has been observed in male rat foetuses. The use of spironolactone tablets in pregnant women requires that the anticipated benefit be weighed against the possible hazards to the mother and foetus.

Breast-feeding

Metabolites of spironolactone have been detected in breast milk. If use of spironolactone tablets is considered essential, an alternative method of infant feeding should be instituted.

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:

General disorders and administration site conditions: malaise

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

Gastrointestinal disorders: gastrointestinal disturbances, nausea

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

Hepatobiliary disorders: hepatic function abnormal

Metabolism and nutrition disorders: electrolyte disturbances, hyperkalaemia

Musculoskeletal disorders: leg cramps

Nervous system disorders: dizziness

Psychiatric disorders: change in libido, confusion

Reproductive system and breast disorders: menstrual disorders, breast pain

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), alopecia, hypertrichosis, pruritus, rash, urticaria,

pemphigoid

Renal and urinary disorders: acute renal failure.

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 at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

Acute overdosage may be manifested by drowsiness, mental confusion, nausea, vomiting, dizziness or diarrhoea. 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. 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, increases sodium excretion whilst reducing potassium loss at the distal renal tubule. It has a gradual and prolonged action.

Severe heart failure: 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 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% to 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 favourable 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

Spironolactone is well absorbed orally and is principally metabolised to active metabolites: sulphur containing metabolites (80%) and partly canrenone (20%). 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). Elimination of metabolites occurs primarily in the urine and secondarily through biliary excretion in the faeces.

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 ($t_{1/2}$) for spironolactone is 2.6 hr., 80 ng/ml, and approximately 1.4 h., 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 $t_{1/2}$ 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.

Paediatric population: There are no pharmacokinetic data available in respect of use in the 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 the potential hazard 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

Maize starch
Calcium sulphate dihydrate
Crospovidone
Povidone
Pregelatinised maize starch
Quinoline yellow lake E104
Peppermint flavour
Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years (36 months)

6.4 Special precautions for storage

Do not store above 25ºC.

Keep container tightly closed (for containers).

Store in the original package (for blisters).

6.5 Nature and contents of container

Cylindrical polypropylene container with polythene lids and polyurethane or polythene inserts, or PVC aluminium foil blister packs enclosed in a cardboard carton.
Packs of 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Relonchem Limited,
Cheshire House,
Gorsey Lane,
Widnes,
Cheshire,
WA8 0RP.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20395/0309

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02/03/2004

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20/02/2019