SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SPIRETIC *25* mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Spironolactone BP 25 mg

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Cirrhosis with ascites and oedema.
2. Malignant ascites
3. Nephrotic syndrome.
4. Diagnosis and treatment of primary hyperaldosteronism.
5. Congestive heart failure.
6. The treatment of hypertension associated with primary hyperaldosteronism.

4.2 Posology and method of administration

Adults:

Prescribing dose once daily with a meal is recommended

Congestive heart failure: Usual dose – 100 mg/day.

In difficult or severe cases the dosage may be gradually increased up to 400 mg/day. When oedema is controlled, the usual maintenance level is 25-200 mg/day.

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

Malignant ascites: Initial dose usually 100-200 mg/day.

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

Nephrotic syndrome: Usual dose – 100-200 mg/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: SPIRETIC may be employed as an initial diagnostic measure to provide presumptive evidence of primary hyperaldosteronism while patients are on normal diets.

Long tests: SPIRETIC is administered at a daily dose of 400 mg for three to four weeks. Correction of hypokalaemia and of hypertension provides presumption evidence for the diagnosis of primary hyperaldosteronism.

Short tests: SPIRETIC is administered at a daily dosage of 400 mg for four days. If serum potassium increases during SPIRETIC administration but drops when SPIRETIC is discontinued a presumptive diagnosis of primary hyperaldosteronism should be considered.

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

Children:

Initial daily dosage should provide 3 mg of spironolactone per kilogram bodyweight, given in divided doses. Dosage should be adjusted on the basis of response and tolerance. If necessary a suspension may be prepared by crushing SPIRETIC tablets. A suitable suspending vehicle is Methylcellulose 20% v/v, purified water to 100%. Such suspension is stable for one month when refrigerated.

Elderly:

Dosage in the elderly should be started with the lowest dose and adjusted on the basis of response and tolerance and may be found to be less than the recommended adult dose.

Route of administration: Oral

4.3 Contraindications

SPIRETIC is contraindicated in patients with anuria, acute renal insufficiency, rapidly progressing impairment of renal function, hyperkalaemia, hyponatraemia, Addison's disease and in patients who are hypersensitive to spironolactone.

4.4 Special warnings and precautions for use

Fluid and electrolyte levels should be monitored, especially in elderly patients and those with significant hepatic or renal impairment. Hepatic coma may be precipitated in susceptible patients.

Hyperkalemia may occur in patients with renal impairment or excessive potassium intake (eg supplements). Spironolactone treatment should be discontinued if hyperkalemia develops. (see section 4.8)

Hyperkalemia or hyponatraemia also may be induced when spironolactone is given with other medicinal products, especially other diuretics (see section 4.5).

Care should be taken in patients with porphyria.

Potentiation of the effect of other anti-hypertensive drugs occurs (see section 4.5) and their dosage should first be reduced by at least 50% when SPIRETIC 100 mg or SPIRETIC 25 mg is added to the treatment regime and then adjusted as necessary.

Carcinogenicity: Spironolactone has been shown to produce tumours in rats when administered at high doses over a long period of time. The significance of those 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.

4.5 Interaction with other medicinal products and other forms of interaction

SPIRETIC should not be administered concurrently with other potassium-conserving diuretics as hyperkalaemia may be induced. Concomitant use of spironolactone with ACE inhibitors, angiotensin II antagonists, aldesterone blockers, ciclosporin and tacrolimus increases the risk of severe hyperkalemia. Indometacin and possibly other NSAIDs also increase the risk of hyperkalaemia.

For the same reason a diet rich in potassium or the use of potassium supplements in association with spironolactone therapy is also not recommended, except in cases of initial potassium depletion. If potassium supplementation is considered essential, serum electrolytes should be monitored.

Hyperkalemia induced by diuretics such as spironolactone increases the risk of ventricular arrythmias when amisulpride, pimozide, sertindole or terfenadine are taken with the diuretic.

Diuretics such as SPIRETIC increase the risk of nephrotoxicity associated with NSAIDS and platimum compounds.

Lithium excretion is decreased by diuretics and therefore the risk of toxicity is increased.

The diuretic effect of spironolactone is antagonised by corticosteroids, oestrogens and NSAIDS (including aspirin, ibuprofen, ketorolac).

An enhanced hypotensive effect is a risk with concomittant use of spironolactone and other antihypertensive agents. In particular with ACE inhibitors, angiotensin II antagonists and l-blockers but also other medicines including andrenergic neurone blockers, antidepressants (MAOI's and tricyclics), l-blockers, calcium channel blockers, anxiolytics & hypnotics, nitrates and phenothiazides.

The effects of cardiac glycosides, such as digoxin, are increased with concomitant use of spironolactone. The digoxin/digitoxin response in patients also receiving SPIRETIC should be monitored by means other than serum concentrations.

Spironolactone antagonizes the ulcer-healing effect of carbenoxolone.

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.

Hyponatraemia may be induced by concomitant use of chlorpropamide, carbamazepine, aminogluthetimide.

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.

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

4.6 Pregnancy and lactation

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

Nursing Mothers: Canrenone, a metabolite of spironolactone, appears in breast milk. If use of SPIRETIC is considered essential, an alternative method of infant feeding should be instituted.

4.7 Effects on ability to drive and use machines

As somnolence and dizziness are possible side effects of spironolactone, patients should exercise caution before driving/operating machinery until their response to initial treatment has been determined.

4.8 Undesirable effects

Gynaecomastia may develop in association with the use of spironolactone and appears to be related to both dosage level and duration of therapy. It is normally reversible upon discontinuing spironolactone treatment, on rare occasions some breast enlargement may persist.

Skin rashes may occur. Pruritus or urticaria also may occur.

Patients receiving spironolactone therapy should be carefully evaluated for possible disturbances of fluid and electrolyte balance.

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 SPIRETIC should be discontinued, and if necessary active measures taken to reduce the serum potassium to normal.

Reversible increase in blood urea has been reported in association with spironolactone therapy, particularly in the presence of impaired renal function.

Dilutional hyponatraemia may be induced, especially when spironolactone is administered in combination with other diuretics.

Other side effects which may occur include:

General: dizziness, headache, mental confusion, drowsiness, lethargy

Gastrointestinal: gastrointestinal disturbances, nausea

Reproductive system: impotence, menstrual irregularities

Urinary system: acute renal failure

Liver disorders: hepatotoxicity, abnormal hepatic function:

Heamatological: leukopenia, thrombocytopenia

Skeletal system: osteomalacia

There have been reports of malignant breast tumours in men.

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

Spironolactone is a steroid which acts on the distal portion of the renal tubule as a competitive inhibiter of aldosterone thereby increasing sodium and water excretion and reducing potassium excretion. It acts as a diuretic.

Spironolactone has a slow onset of action requiring two or three days for maximum effect.

5.2 Pharmacokinetic properties

Spironolactone is incompletely but fairly rapidly absorbed from the gastro-intestinal tract, the extent of absorption depending on particle size and formulation. Canrenone, which is an active metabolite, has biphasic plasma half-life of about 4 and 17 hours. Spironolactone is excreted in the urine and in the faeces, in the form of metabolites. It is extensively bound to plasma proteins. Spironolactone or its metabolites may cross the placental barrier, and canrenone is excreted in breast milk.

5.3 Preclinical safety data

See information in Section 4.4. regarding carcinogenicity. Teratogenicity studies in animals have shown feminisation of the male 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

36 months

6.4 Special precautions for storage

Store in a dry place below 25ºC.
Keep container well closed
Keep out of reach of children

6.5 Nature and contents of container

1. High density polystyrene with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane or polythene inserts.
   Packs of 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000 tablets.

2. PVC aluminium foil blister packs.
   Packs of 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000 tablets.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

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NICOSIA
CYPRUS
P.C. 1060
CYPRUS

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PL 33414/0105

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19/01/1984 11/6/1996

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04/04/2025