SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Lactone – 25 (Spironolactone 25mg Film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 25 mg spironolactone.

Excipient(s) with known effect:

Each tablet contains 109.15 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablet

Yellow colored, circular, biconvex film coated tablets engraved as 'LACTON 25' on one side and plain on the other side.

4. CLINICAL PARTICULAR

4.1 Therapeutic Indications:

- Congestive heart failure
- Nephrotic syndrome
- Hepatic cirrhosis with ascites and oedema
- Malignant ascites
- The diagnosis and treatment of primary aldosteronism

Children should only be treated under guidance of a pediatric specialist.

4.2 Posology and Method of Administration

Posology

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

Adults:

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 ≤5.0 mEq/L and serum creatinine is ≤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.

Hepatic cirrhosis with ascites and oedema: If urinary Na+/K+ ratio is greater than 1.0; 100mg daily. If the ratio is less than 1.0; 200-400mg daily. Maintenance doses should be individually determined.

Malignant ascites: Initial dosage is usually 100-200mg daily. In severe cases the dosage may be gradually increased up to 400mg daily. When oedema is controlled, dosage should be individually determined.

Nephrotic syndrome: Usually 100-200mg daily. 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 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 3-4 weeks. Correction of hypokalaemia and of 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 the diagnosis of hyperaldosteronism has been established by more definitive testing procedures, spironolactone may be administered in doses of 100-400mg daily in preparation for surgery. For patients who are considered unsuitable for surgery, spironolactone may be employed for long-term maintenance therapy at the lowest effective dosage determined for the individual patient.

Elderly: It is recommended that treatment should commence with the lowest dose and be titrated upwards as required in order to achieve maximum benefit. Caution should be exercised in severe hepatic and renal impairment which may alter drug metabolism and excretion.

Paediatric population:

Initially daily dosage should provide 1-3mg of spironolactone per kg bodyweight in divided doses. Dosage should be adjusted in accordance with response and tolerance. 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.

Method of Administration: For oral administration.

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

4.3 Contraindications

Spironolactone therapy is contraindicated in the following:

- Hypersensitivity to the active substance or to any of the excipients
- Anuria (patients are at greater risk of developing hyperkalaemia)
- Active renal insufficiency, rapidly progressing or severe 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
- 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:

Patients receiving spironolactone should be carefully evaluated for possible disturbances of fluid and electrolyte balance, 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. Dilutional hyponatraemia may be induced especially when spironolactone is concurrently administered with other diuretics.

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 tablets 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. Care should be taken in patients suffering from hyponatraemia.

Urea: Reversible increases in blood urea have been reported 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.

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;

Excipients: Lactose

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

Information on sodium content:

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

Abiraterone: 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.

ACE inhibitors: since ACE inhibitors decrease aldosterone production they should not routinely be used with spironolactone, particularly in patients with marked renal impairment.

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

Antihypertensive 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.

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.

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

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 normalized ratio) should be monitored with the addition and withdrawal of treatment with spironolactone, and should be reassessed periodically during 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-sparing diuretics as this may induce hyperkalaemia. Potassium canrenoate, a metabolite of spironolactone, has been shown to cause myeloid leukaemia in rats.

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 five to seven days of adding or discontinuing spironolactone and periodically thereafter. Lower lithium doses may be required with concomitant spironolactone therapy.

NSAIDs: 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/particularly indometacin are used with spironolactone. Indometacin and mefenamic acid inhibit the excretion of canrenone reducing the diuretic effect.

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

Sympathomimetics: Spironolactone reduces vascular responsiveness to noradrenaline (norepinephrine). Caution should be exercised in the management patients subjected to regional or general anaesthesia.

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

Ulcer healing drugs: As carbenoxolone may cause sodium retention and thus decrease the effectiveness of spironolactone, concurrent use of the two agents should be avoided.

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

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

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. Spironolactone should be used with caution in pregnant women, weighing the potential risk to the mother and foetus against the possible benefits.

Breast-feeding

Canrenone, a metabolite of spironolactone, appears in breast milk, therefore an alternative method of infant feeding should be instituted.

4.7 Effects on ability to drive and use machines

Patients should be warned that they may experience somnolence, dizziness or drowsiness when taking this medicine. They should make sure they are not affected before driving or operating machinery.

4.8 Undesirable effects

• **Neoplasms benign, malignant and unspecified (including cysts and polps):** benign breast neoplasm

• **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.

• **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.

• **Metabolism and nutrition disorders:** hyperkalemia and hyponatraemia has been reported rarely. Electrolyte disturbances.

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

• **Psychiatric disorders:** lethargy, changes in libido, confusion.

• **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.

• **Hepato - biliary disorders:** hepatic function abnormal, hepatotoxicity has been reported.

• **Gastrointestinal disorders:** gastritis, gastric bleeding, gastrointestinal disturbances, stomach cramps, diarrhoea, vomiting, nausea and ulceration are more frequent effects.

• **Skin and subcutaneous tissue disorders:** Pemphigoid, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS)

have been reported. Urticaria, hypertrichosis, pruritus, rash and alopecia has been reported rarely.

• **Musculoskeletal, connective tissue and bone disorders:** leg cramps, osteomalacia.

• **Renal and urinary disorders:** acute renal failure, particularly in those with pre-existing renal impairment.

• **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 usually reversible once therapy 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 have been reported. This is usually reversible on discontinuation of spironolactone. Breast tenderness and increased hair growth in females, irregular menstrual periods and sweating have been reported.

4.9 Over Dosage:

Toxic effects of overdosage are 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, lassitude and muscular weakness, flaccid paralysis or muscle spasm and may be difficult to distinguish clinically from hypokalaemia.

No specific antidote has been identified. Improvement may be expected on cessation of therapy. Electrocardiographic changes are the earliest specific signs of potassium disturbances. General supportive measures 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: Potassium-sparing Agents, **ATC code:** C03D A01

Mechanism of action

Spironolactone is a steroid with a structure resembling that of the natural adrenocorticoid hormone, aldosterone. It acts as a competitive inhibitor of aldosterone and acts on the distal portion of the renal tubule thereby increasing sodium and water excretion and reducing potassium excretion.

It has a gradual and prolonged action.It is classed as a potassium sparing diuretic or aldosterone antagonist.

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 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

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 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% sulfur containing metabolities such as 7 alpha-thiomethylspironolactone and canrenone (20%). Many of these metabolities 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.

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., 80 ng/ml, and approximately 1.4 hr., 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.

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

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

Lactose Monohydrate

Pregelatinized starch

Microcrystalline Cellulose (PH 101)

Sodium Starch Glycolate BP (Type A)

Povidone (K-30)

Microcrystalline Cellulose (PH 102)

Peppermint HI-FI PF (2917M)

Magnesium Stearate

Hypromellose (5 CPS)

Titanium Dioxide

Purified Talc

Macrogol (6000)

Ferric Oxide Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30°C in the original package in order to protect from moisture.

6.5 Nature and Contents of Container

Printed Aluminum Foil/Clear PVDC Film

Blister Pack :10 x 10 Tablets

6.6 Special precautions for disposal and other handling

No Special Requirements

7. MARKETING AUTHORIZATION HOLDER

M/S BAFNA PHARMACEUTICALS LTD
Bafna Towers,
299, Thambu Chetty Street,
Chennai – 600001,
India.
Tel No:044-25267517/25270992/42677555

8. MARKETING AUTHORIZATION NUMBER

07352/07716/NMR/2019

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

04/05/2022

10. DATE OF REVISION OF THE TEXT

12/07/2023

11. REFERENCES