For the use only of a Registered Medical Practitioner or Hospital or a Laboratory.

This package insert is continually updated: Please read carefully before using a new pack

Frusemide and Spironolactone Tablets
Lasilactone® 50

COMPOSITION

Each film coated tablet contains
Frusemide I.P. …….. 20mg
Spironolactone I.P…..50mg

THERAPEUTIC INDICATIONS

Lasilactone® contains a short-acting diuretic and a long-acting aldosterone antagonist. It is indicated in the treatment of resistant oedema where this is associated with secondary hyperaldosteronism; conditions include chronic congestive cardiac failure and hepatic cirrhosis.

Treatment with Lasilactone® should be reserved for cases refractory to a diuretic alone at conventional doses.

This fixed ratio combination should only be used if titration with the component drugs separately indicates that this product is appropriate.

The use of Lasilactone® in the management of essential hypertension should be restricted to patients with demonstrated hyperaldosteronism. It is recommended that in these patients also, this combination should only be used if titration with the component drugs separately indicates that this product is appropriate.

POSOLOGY AND METHOD OF ADMINISTRATION

For oral administration.
The dose must be the lowest that is sufficient to achieve the desired effect.

Adults: 1-4 tablets daily.

Children: The product is not suitable for use in children.

Elderly: Frusemide and Spironolactone may both be excreted more slowly in the elderly.

Tablets are best taken at breakfast and/or lunch with a generous amount of liquid (approx. 1 glass). An evening dose is not recommended, especially during initial treatment, because of the increased nocturnal output of urine to be expected in such cases.

CONTRAINDICATIONS

Lasilactone® must not be used:

- in patients with hypersensitivity to frusemide, spironolactone or any of the excipients of Lasilactone®. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to frusemide.
- in patients with hypovolaemia or dehydration.
- in patients with anuric renal failure not responding to frusemide
- in patients with severe hypokalaemia,see “ADVERSE REACTIONS”
- in patients with severe hyponatraemia.
- in patients with pre-comatose and comatose states associated with hepatic encephalopathy.

- in patients with impaired renal function and a creatinine clearance below 30 ml/min per 1.73 m^2 body surface area, acute renal failure, or anuria.
- during pregnancy (see section, 'Pregnancy and Lactation').
- in breast-feeding women (see section, 'Pregnancy and Lactation').
- in patients with hyperkalaemia

WARNINGS

Spironolactone:
Spironolactone may cause vocal changes. In determining whether to initiate treatment with Lasilactone®, special attention must be given to this possibility in patients whose voice is particularly important for their work (e.g., actors, singers, teachers).

PRECAUTIONS

Frusemide
Urinary outflow must be secured.In patients with a partial obstruction of urinary outflow (e.g in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra), increased production of urine may provoke or aggravate complaints.

Thus, these patients require careful monitoring - especially during the initial stages of treatment.

Treatment with Lasilactone® necessitates regular medical supervision. Particularly careful monitoring is necessary
- in patients with hypotension.
- in patients who would be at particular risk from a pronounced fall in blood pressure, e.g. patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain.
- in patients with latent or manifest diabetes mellitus.
- in patients with gout.
- in patients with hepatorenal syndrome, i.e. functional renal failure associated with severe liver disease.
- in patients with hypoproteinaemia, e.g. associated with nephrotic syndrome (the effect of frusemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- in premature infants (possible development nephrocalcinosis / nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

Regular monitoring of serum sodium, potassium and creatinine is generally recommended during frusemide therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss (e.g. due to vomiting, diarrhoea or intense sweating). Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of frusemide.

<u>Concomitant use with risperidone</u>
In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or frusemide alone (4.1%; mean age 80 years, range 67-90 years).

Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to

the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (see Contraindications).

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

Spironolactone:
Treatment with Lasilactone® necessitates regular medical supervision.

Particularly careful monitoring is necessary
- in patients with severe hypotension.
- in patients with reduced renal function (increased risk of development of hyperkalaemia).

Treatment with Lasilactone® requires regular monitoring of serum sodium, potassium, and creatinine.

Frequent checks of the serum potassium level are necessary in patients with impaired renal function and a creatinine clearance below 60 ml/min per 1.73 m^2 body surface area as well as in cases where Lasilactone® is taken in combination with certain other drugs which may lead to an increase in potassium concentration.
For some patients with metastatic castration-resistant prostate cancer, tumor progression has been observed during spironolactone treatment. Spironolactone binds to the androgen receptor and can increase the prostate-specific antigen (PSA) value.

INTERACTIONS

Frusemide:

Drug Interactions
Not recommended associations
In isolated cases intravenous administration of furosemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of furosemide concomitantly with chloral hydrate is, therefore, not recommended.

Frusemide may potentiate the ototoxicity of aminoglycosides and other ototoxic drugs. Since this may lead to irreversible damage, these drugs must only be used with frusemide if there are compelling medical reasons.

Precautions for use
There is a risk of ototoxic effects if cisplatin and frusemide are given concomitantly. In addition, nephrotoxicity of cisplatin may be enhanced if frusemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Oral frusemide and sucralfate must not be taken within 2 hours of each other because sucralfate decreases the absorption of frusemide from the intestine and so reduces its effect.

Frusemide decreases the excretion of lithium salts and may cause increased serum lithium levels, resulting in increased risk of lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored in patients receiving this combination.

Patients who are receiving diuretics may suffer severe hypotension and deterioration in renal function, including cases of renal failure, especially when an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor antagonist is given for the first time or for the first time in an increased dose. Consideration must be given to interrupting the administration of

frusemide temporarily or at least reducing the dose of frusemide for three days before starting treatment with, or increasing the dose of, an ACE inhibitor or angiotensin II receptor antagonist.

Risperidone: Caution should be exercised and the risks and benefits of the combination or cotreatment with frusemide or with other potent diuretics should be considered prior to the decision to use. See Precautions, regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Levothyroxine: High doses of frusemide may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.

Take into account
Concomitant administration of non-steroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the effect of frusemide. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by frusemide.

Attenuation of the effect of frusemide may occur following concurrent administration of phenytoin.

Corticosteroids, carbenoxolone, liquorice in large amounts, and prolonged use of laxatives may increase the risk of developing hypokalaemia.

Some electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome).

If antihypertensive agents, diuretics or other drugs with blood-pressure-lowering potential are given concomitantly with frusemide, a more pronounced fall in blood pressure must be anticipated.

Probenecid, methotrexate and other drugs which, like frusemide, undergo significant renal tubular secretion may reduce the effect of frusemide. Conversely, frusemide may decrease renal elimination of these drugs. In case of high-dose treatment (in particular, of both frusemide and the other drugs), this may lead to increased serum levels and an increased risk of adverse effects due to frusemide or the concomitant medication.

The effects of antidiabetic drugs and blood-pressure-increasing sympathomimetics (e.g. epinephrine, norepinephrine) may be reduced. The effects of curare-type muscle relaxants or of theophylline may be increased.

The harmful effects of nephrotoxic drugs on the kidney may be increased.

Impairment of renal function may develop in patients receiving concurrent treatment with frusemide and high doses of certain cephalosporins.

Concomitant use of cyclosporine A and frusemide is associated with increased risk of gouty arthritis secondary to frusemide-induced hyperuricaemia and cyclosporine impairment of renal urate excretion.

Patients who were at high risk for radiocontrast nephropathy treated with frusemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high risk patients who received only intravenous hydration prior to receiving radiocontrast.

Spironolactone:

Food
Absorption of spironolactone is increased if Lasilactone is taken together with food. The clinical relevance of this interaction is unknown.

Not recommended associations
When spironolactone is taken in combination with potassium salts, with drugs which reduce potassium excretion, with nonsteroidal anti-inflammatory drugs or with ACE inhibitors, an increase in serum potassium concentration and severe hyperkalaemia may occur.

Take into account
Concurrent administration of nonsteroidal anti-inflammatory drugs may weaken the action of spironolactone.

Both spironolactone and carbenoxolone may impair the action of the other substance. In this regard, liquorice in larger amounts acts in the same manner as carbenoxolone.

Spironolactone may cause raised blood digoxin levels.

If other blood-pressure-lowering drugs are taken concurrently with Lasilactone®, a more pronounced fall in blood pressure must be anticipated.

Cholestyramine: Hyperkalaemia could occur in the context of hyperchloraemic metabolic acidosis in patients given Lasilactone® concurrently with cholestyramine.

PREGNANCY AND LACTATION

Pregnancy:
Lasilactone® must not be taken during pregnancy.

Lactation:
Breast-feeding must be avoided during treatment with Lasilactone®

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

Frusemide
Some adverse effects (e.g. an undesirably pronounced fall in blood pressure) may impair the patient's ability to concentrate and react, and, therefore, constitute a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

Spironolactone
In association with various adverse reactions, powers of concentration and reaction may be impaired during treatment with Lasilactone®, affecting the patient's ability, for example, to operate a vehicle or machinery. This applies especially at the commencement of treatment or after consumption of alcohol.

ADVERSE REACTIONS

Frusemide

The frequencies are derived from literature data referring to studies where frusemide is used in a total of 1387 patients, at any dose and in any indication. When the frequency category for the same ADR was different, the highest frequency category was selected.

The following CIOMS frequency rating is used, when applicable: Very common ≥ 10 %; Common ≥ 1 and <10 % ; Uncommon ≥ 0.1 and < 1 %;Rare ≥ 0.01 and < 0.1 %; Very rare < 0.01 %, Unknown Not known (cannot be estimated from available data).

- Metabolism and nutrition disorders(See section “precautions”)
    - Very common: electrolyte disturbances (including symptomatic), dehydration , hypovolaemia especially in elderly patients, blood creatinine increased, blood triglyceride increased.

- Common : hyponatremia, hypochloremia, hypokalaemia, blood cholesterol increased, blood uric acid increased and attacks of gout,
- Uncommon: glucose tolerance impaired. Latent diabetes mellitus may become manifest. (See section “Precautions”)
- Not known : hypocalcemia, hypomagnesemia, blood urea increased , metabolic alkalosis
- Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide.

- Vascular disorders
  - Very common (for intravenous infusion) : hypotension including orthostatic hypotension(see section “Precautions”)
  - Rare : vasculitis
  - Not known : thrombosis

- Renal and urinary disorders
  - Common : urine volume increased
  - Rare : tubulointerstitial nephritis
  - Not known:
    - urine sodium increased, urine chloride increase, urine retention (in patients with a partial obstruction of urinary outflow see section “Precautions”)
    - nephrocalcinosis/nephrolithiasis in premature infants(see section “Precautions”)
    - renal failure(See section “Interactions”)

- Gastrointestinal disorders
  - Uncommon : nausea,
  - Rare : vomiting, diarrhoea
  - Very rare : pancreatitis acute

- Hepato-biliary disorders
  - Very rare : cholestasis, transaminases increased

- Ear and labyrinth disorders
  - Uncommon: hearing disorders although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephrotic syndrome) and/or when intravenous furosemide has been given too rapidly. Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide
  - Rare : tinnitus

- Skin and subcutaneous tissue disorders
  - Uncommon : pruritus, urticaria, rashes, dermatitis bullous, erythema multiforme, pemphigoid, dermatitis exfoliative, purpura, photosensitivity reaction
  - Not known : Stevens-Johnson syndrome, toxic epidermal necrolysis(4), AGEP (acute generalized exanthematous pustulosis)(5) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), lichenoid reactions

- Immune system disorders
  - Rare : severe anaphylactic or anaphylactoid reactions (e.g. with shock)
  - Not known: exacerbation or activation of systemic lupus erythematosus.

- Nervous system disorders
  - Rare : paraesthesia
  - Common : hepatic encephalopathy in patients with hepatocellular insufficiency(See section “Contraindications”)
  - Not known: dizziness, fainting or loss of consciousness, headache

- Blood and the lymphatic system disorders
  - Common : haemoconcentration
  - Uncommon : thrombocytopenia,
  - Rare : leucopenia, eosinophilia
  - Very rare : agranulocytosis, aplastic anaemia or haemolytic anaemia

- Musculoskeletal and connective tissue disorders
    - Not known: cases of rhabdomyolysis have been reported, often in the context of severe hypokalaemia (see “CONTRAINDICATIONS”)

- Congenital and familial/genetic disorders
    - Not known: increased risk of persistence of patent ductus arteriosus when frusemide is administered to premature infants during the first weeks of life.

- General disorders and administration site conditions
    - Not known : following intramuscular injection, local reactions such as pain
    - Rare : fever

Spironolactone

Frequencies for the following adverse reactions are not known (cannot be estimated from available data).

Blood and lymphatic system disorders
Changes in the blood picture (e.g. eosinophilia, agranulocytosis).

Gastrointestinal disorders
Gastrointestinal symptoms such as nausea, vomiting or diarrhoea ;. an increase in liver enzyme levels as well as gastric ulceration (also with bleeding), may develop.

Hepatobiliary disorders
Hepatitis

Metabolism and nutrition disorders
In the course of treatment with spironolactone, hyperkalaemia may develop. This possibility is particularly acute in patients with renal function disturbances. Particularly in the event of an irregular pulse, tiredness or muscle weakness (e.g. in the legs), careful consideration must be given to the possibility of hyperkalaemia.

Spironolactone may lead to hyponatraemia (particularly in conjunction with administration or ingestion of abundant quantities of water), to hypovolaemia and to dehydration, and contribute to the development or worsening of a hyperchloraemic metabolic acidosis.

Dizziness or leg cramps in the context of hypovolaemia, dehydration or hyperkalaemia may also occur.

Various diseases, other concomitant medication as well as the type of nutrition may play an important role in the possible development of disturbances in electrolyte balance.

Disturbances in electrolyte balance - particularly if pronounced - must be corrected.

Nervous system disorders
Headache, ataxia, drowsiness/somnolence, lethargy

Renal and urinary disorders
Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow, renal failure especially in the context of decreased renal perfusion.

Reproductive system and breast disorders
Because of its chemical similarity to the sex hormones, spironolactone may make the nipples more sensitive to touch and cause mastodynia and enlargement of the breasts. This effect is dose-dependent and occurs in both men and women. Enlargement of the breasts in men is therapy duration-dependent and reversible.

In women, menstrual irregularities (dose-dependent). including amenorrhea.

In men, potency may be impaired.
Progression of castration-resistant prostate cancer

Respiratory, thoracic and mediastinal disorders
Rarely, spironolactone may cause vocal changes in the form of hoarseness and (in women) deepening of the voice or (in men) increase in pitch. In some patients these vocal changes persist even after Lasilactone® has been discontinued.

Skin and subcutaneous tissue disorders
Spironolactone may trigger allergic or allergy-like skin reactions (among others, urticaria, pruritus)

Bullous pemphigoid, hirsutism.

OVERDOSE

Frusemide
The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias (including A V block and ventricular fibrillation). Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

No specific antidote to frusemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designed to reduce absorption (e.g. activated charcoal).

Clinically relevant disturbances in electrolyte and fluid balance must be corrected. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures.

Spironolactone
Possible signs of an overdose or intoxication may include disturbances in electrolyte and fluid balances, and symptoms such as somnolence and confusion.

No specific antidote is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient through measures for primary detoxification (e.g. gastric lavage) or those designed to reduce absorption (e.g. activated charcoal).

Clinically relevant disturbances in electrolyte and fluid balance must be corrected. This corrective action as well as the prevention and treatment of serious complications resulting from such disorders (e.g. hyperkalaemia) and of other effects on the body may necessitate general and specific intensive medical monitoring and therapeutic measures (e.g. potassium elimination).

Expiry date
Do not use later than the date of expiry

Storage
Store in a cool dry place. Protect from light

Keep medicine out of reach of children.

Manufactured by:
Sanofi India Limited, GIDC Estate, Post Box 136, Ankleshwar 393002, India.

Dated: - Jan 2018

References:

1) Spironolactone CCDS Version 05 dated 26th October 2017
2) Frusemide - CCDS version 12 dated 23rd June 2017
3) Lasilactone Capsule UK SPC dated Nov 2016