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

For Frusemide and Spironolactone:

Lasilactone® must not be used:

- in patients with hypovolaemia or dehydration.
- 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.
- in patients with hyperkalaemia
- in patients with severe hypokalaemia,
- in patients with severe hyponatraemia
- in patients with pre-comatose and comatose states associated with hepatic encephalopathy.

- in lactating women.
- during pregnancy (for spironolactone component).
- in patients with hypersensitivity to frusemide, spironolactone or any of the excipients of Lasilactone®.

For Frusemide:

Lasilactone® must not be used:
- Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to frusemide.

WARNINGS/PRECAUTIONS

Related to Lasilactone
There has been no experience with Lasilactone in children. Its use in children is not recommended.
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.

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.

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.

Related to Frusemide
The possibility exists of exacerbation or activation of systemic lupus erythematosus.

Concomitant use:
Risperidone
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.

Particularly careful monitoring is necessary**:**

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.

Related to Spironolactone:
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. (also see Interactions)

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).

Particularly careful monitoring is necessary:
In patients with reduced renal function (increased risk of development of hyperkalaemia).

INTERACTIONS

Related to Lasilactone

Concomitant use: Take into account
If antihypertensive agents, diuretics or other drugs with blood-pressure-lowering potential are given concomitantly with Lasilactone, a more pronounced fall in blood pressure must be anticipated.
Concomitant administration of non-steroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the effect of Lasilactone. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by frusemide.

Related to Frusemide component:
Food:
It is recommended that oral formulations of frusemide be taken on an empty stomach. Whether and to what extent the absorption of frusemide is affected by taking it with food seems to depend on the pharmaceutical formulation

Not recommended associations

In isolated cases intravenous administration of frusemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of frusemide 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.

Precaution 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 co-treatment with frusemide or with other potent diuretics should be considered prior to the decision to use. See Section Warnings/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.

Concomitant use: Take into account

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.

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

Aliskiren reduces plasma concentration of furosemide given orally. In patients treated with both aliskiren and oral furosemide, it is recommended to monitor for reduced diuretic effect and adjust the dose accordingly.

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).
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.

Related to Spironolactone Component
Food:
Absorption of spironolactone is increased if Lasilactone is taken together with food.

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.

Concomitant use: Take into account

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

Concomitant use of spironolactone and carbenoxolone may produce the effect of reciprocally altering the action of the drugs. In this sense, liquorice in large amounts acts in the same way as carbenoxolone.

Spironolactone may cause raised blood digoxin levels.

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.[i]

REPRODUCTION

Pregnancy:
Lasilactone® must not be given during pregnancy (See Section Contraindications).

Frusemide crosses the placental barrier.

Animal studies conducted with spironolactone have shown genital feminization in male offspring. Anti-androgenic effects have been reported in human under risk of external genital ambiguity in new-born males

Lactation:
Use of Lasilactone is contraindicated during lactation (see Section Contraindications).
Frusemide passes into the breast milk and inhibits lactation.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS

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).

ADVERSE REACTIONS

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 %, Not known (cannot be estimated from available data).

Related to Lasilactone

• *Metabolism and Nutrition disorders*
Common: Hyponatremia

• *Renal and urinary Disorder*
Urine volume increased, urine retention (in patients with a partial obstruction of urinary outflow), renal failure

• *Nervous System disorders*
Headache

• *Gastrointestinal disorders*
Nausea, vomiting, diarrhoea

• *Hepatobiliary disorders*
Hepatic Enzyme increased

Related to Frusemide:

• *Blood and lymphatic systems disorders*
Haemoconcentration, thrombocytopenia, leucopenia, eosinophilia, agranulocytosis, aplastic anaemia or haemolytic anaemia

• *Metabolism and nutrition disorder*
Very common: Electrolyte disturbances (including symptomatic), dehydration, hypovolaemia, especially in elderly patients

Investigations in Metabolism and nutrition disorder: Blood urea increased, blood creatinine increased, blood triglyceride increased, hypochloremia, blood cholesterol increased, urine chloride increase, urine sodium increased

Hypokalaemia, hypocalcemia, hypomagnesemia, metabolic alkalosis

Pseudo-Bartter syndrome in the context of misuse and/or long-term use of frusemide.
Blood uric acid increased and attacks of gout
Glucose tolerance impaired. Latent diabetes mellitus may become manifest.

• *Renal and urinary Disorders*
Tubulointerstitial nephritis
Not known: Nephrocalcinosis/nephrolithiasis in premature infants

• *Vascular disorders*
Hypotension including orthostatic hypotension, vasculitis, thrombosis

• *Gastrointestinal disorders*
Acute pancreatitis

• *Hepatobiliary disorders*
Cholestasis

• *Ear and Labyrinth disorders*
Hearing disorders although usually transitory, particularly in patients with renal failure, hypoproteinaemia (e.g. in nephrotic syndrome), Tinnitus.
Deafness, sometimes irreversible cases have been reported.

• *Immune System disorders*
Pruritus, urticaria, rashes, dermatitis bullous, erythema multiforme, pemphigoid, dermatitis exfoliative, purpura, photosensitivity reaction, lichenoid reactions, severe anaphylactic or anaphylactoid reactions (e.g. with shock), exacerbation or activation of systemic lupus erythematosus.

• *Skin and Subcutaneous tissue disorders*
Stevens-Johnson syndrome, toxic epidermal necrolysis, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms).

• *Nervous System disorders*
Paraesthesia, hepatic encephalopathy in patients with hepatocellular insufficiency, dizziness, fainting or loss of consciousness

• *Musculoskeletal and connective tissue disorders*
Rhabdomyolysis cases have been reported, often in the context of severe hypokalaemia.

• *Congenital, familial/genetic disorders*
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
Fever
Related to Spironolactone:
Frequencies for the following adverse reactions are not known (cannot be estimated from available data).

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

• *Metabolism and nutrition disorders*
Lasilactone may lead to hypovolaemia and to dehydration, and contribute to the development or worsening of a hyperchloraemic metabolic acidosis.
Hypovolaemia may occur as a result of excessive diuresis. This may manifest as anorexia, dry mouth and thirst, vomiting, headache or feelings of pressure in the head, asthenia, drowsiness, visual disturbances, apathy, confusional states, and circulatory disturbances.
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.

Hyperkalaemia- Hyperkalaemia 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.

• *Gastrointestinal disorder*
Gastric ulceration (also with bleeding) may develop.

• *Hepatobiliary disorder*
Hepatitis

• *Immune System disorder*
Allergic or allergy-like skin reactions (among others, urticaria, pruritus), Bullous pemphigoid.

• *Skin and Subcutaneous tissue disorder*
Hirsutism,

• *Nervous System disorder*
Drowsiness/somnolence, lethargy, ataxia.

• *Reproductive systems and breast disorder*
In women, menstrual irregularities (dose-dependent) including amenorrhea.
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.

Erectile dysfunction
Progression of castration-resistant prostate cancer.

Respiratory, thoracic and mediastinal disorder
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.

OVERDOSE
SIGNS AND SYMPTOMS
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 due to excessive diuresis. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

MANAGEMENT
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 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.

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,
At Plot no. 3501-15, 6301-13 & 16, meter road I/c, GIDC Estate,
Ankleshwar-393002, Gujarat

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Source:

1. Furosemide + Spironolactone, CCDS version 3 dated 08 July 2022
2. Lasilactone 20/50 mg Capsules UK SPC revision date 15th December 2021 accessed on 27th February 2022 (for dosage and indications)