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

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

Frusemide Tablets I.P. 40mg
Frusemide Injection I.P.

Lasix®

THERAPEUTIC OR PHARMACOLOGICAL CLASS
Loop diuretic; Antihypertensive.

PHARMACEUTICAL FORM(S)
Tablets, Solution for injection and Solution for infusion.

COMPOSITION
Lasix Tablets 40mg
Each uncoated tablet contains Frusemide I.P. 40 mg

Lasix Injection 2ml
Each ml contains Frusemide I.P. 10mg
Water for Injection I.P. qs

Lasix Injection 4ml
Each ml contains Frusemide I.P. 10mg
Water for Injection I.P. qs

INDICATIONS
- Fluid retention associated with chronic congestive cardiac failure (if diuretic treatment is required).
- Fluid retention associated with acute congestive cardiac failure.
- Fluid retention associated with chronic renal failure.
- Maintenance of fluid excretion in acute renal failure, including that due to pregnancy or burns.
- Fluid retention associated with nephrotic syndrome (if diuretic treatment is required).
- Fluid retention associated with liver disease (if necessary to supplement treatment with aldosterone antagonists).
- Hypertension.
- Hypertensive crisis (as a supportive measure).
- Support of forced diuresis.

DOSAGE AND ADMINISTRATION

General
The dose used must be the lowest that is sufficient to achieve the desired effect.

Frusemide is given intravenously only when oral administration is not feasible or is ineffective (e.g. in impaired intestinal absorption) or if a rapid effect is required. If intravenous therapy is used, it is recommended that transfer to oral therapy be carried out as soon as possible.

To achieve optimum efficacy and suppress counter-regulation, a continuous Frusemide infusion is generally to be preferred to repeated bolus injections. Where continuous Frusemide infusion is not feasible for follow-up treatment after one or several acute bolus doses, a follow-up regimen with low

doses given at short intervals (approximately 4 hours) is to be preferred to a regimen with higher bolus doses at longer intervals.

In adults, the recommended maximum daily dose of Frusemide for both oral and intravenous administration is 1500 mg.

The duration of treatment depends on the indication and is determined on an individual basis by the physician.

Special Populations
Special dosage recommendations

Children
In children dosage is to be reduced in relation to body weight.
In children, the recommended dose of Frusemide for oral administration is 2 mg/kg body weight up to a maximum daily dose of 40 mg.
The recommended dose of Frusemide for parenteral administration is 1 mg/kg body weight up to a maximum daily dose of 20 mg.

Adults

- **Hepatic impairment: Fluid retention associated with liver disease**

Frusemide is used to supplement treatment with aldosterone antagonists in cases where these alone are not sufficient. In order to avoid complications such as orthostatic intolerance or electrolyte and acid-base imbalances, the dose must be carefully titrated so that the initial loss of fluid is gradual. For adults, this means a dose which leads to a loss of approximately 0.5 kg body weight per day.

The recommended initial oral dose is 20 mg to 80 mg daily. This may be adjusted as necessary according to response. The daily dose may be given as a single dose or divided doses. If intravenous treatment is absolutely necessary, the initial single dose is 20 mg to 40 mg.

- **Renal impairment: Fluid retention associated with chronic renal failure**

The natriuretic response to Frusemide depends on a number of factors, including severity of renal failure and the sodium balance, and, therefore, the effect of a dose cannot be accurately predicted. In patients with chronic renal failure, the dose must be carefully titrated so that the initial loss of fluid is gradual. For adults, this means a dose which leads to a loss of approximately 2 kg body weight (approximately 280 mmol Na+) per day.

The recommended initial oral dose is 40 mg to 80 mg daily. This may be adjusted as necessary according to response. The total daily dose may be given as a single dose or two divided doses.

In dialysis patients, the usual oral maintenance dose is 250 mg to 1500 mg daily.

In intravenous treatment, the dose of Frusemide may be determined by starting with a continuous intravenous infusion of 0.1 mg per minute and then gradually increasing the rate every half hour according to response.

- **Renal impairment: Maintenance of fluid excretion in acute renal failure**

Hypovolaemia, hypotension, and significant electrolyte and acid-base imbalances must be corrected before starting Frusemide. It is recommended that transfer from the intravenous to the oral route of administration is carried out as soon as possible.

The recommended initial dose is 40 mg given as an intravenous injection. If this does not lead to the desired increase in fluid excretion, Frusemide may be given as a continuous intravenous infusion, starting with a rate of 50 mg to 100 mg per hour.

- **Renal impairment: Fluid retention associated with nephrotic syndrome**

The recommended initial oral dose is 40 mg to 80 mg daily. This may be adjusted as necessary according to response. The total daily dose may be given as a single dose or several divided doses. (See PRECAUTIONS)

- **Fluid retention associated with chronic congestive cardiac failure**

The recommended initial oral dose is 20 mg to 80 mg daily. This may be adjusted as necessary according to response. It is recommended that the daily dose is given as two or three divided doses.

- **Fluid retention associated with acute congestive cardiac failure**

The recommended initial dose is 20 to 40 mg given as an intravenous bolus injection. The dose may be adjusted as necessary according to response.

- **Hypertension**

Frusemide can be used alone or in combination with other antihypertensive agents.
The usual oral maintenance dose is 20 mg to 40 mg daily. In hypertension associated with chronic renal failure, higher doses may be required.

- **Hypertensive crisis**

The recommended initial dose of 20 mg to 40 mg is given as an intravenous bolus injection. This may be adjusted as necessary according to response.

- **Support of forced diuresis in poisoning**

Frusemide is given intravenously in addition to infusions of electrolyte solutions. The dose is dependent on the response to frusemide. Fluid and electrolyte losses must be corrected before and during treatment.

In case of poisoning with acid or alkaline substances, elimination can be increased further by alkalization or acidification respectively, of the urine.

The recommended initial dose is 20 mg to 40 mg given intravenously.

ADMINISTRATION

Oral formulations:
It is recommended that Lasix® be taken on an empty stomach. Tablets are to be swallowed without chewing and with sufficient amounts of liquid.

Intravenous injection/infusion:
Intravenous frusemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine >5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

Intramuscular injection:
Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration is feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary oedema.

CONTRAINDICATIONS

Lasix® must not be used:

- in patients with hypersensitivity to frusemide or any of the excipients of Lasix®. 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 breast-feeding women.

Concerning use during pregnancy, see “PREGNANCY”

PRECAUTIONS

Urinary outflow must be secured.
In patients with partial obstruction of urinary outflow (e.g in patients with bladder – emptying disorders, prostatic hyperplasia, 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 Lasix® 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.

Concomitant use with 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 (see CONTRAINDICATIONS).

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

INTERACTIONS

Food

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

Drug interactions

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.

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 co-treatment 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.

PREGNANCY

Frusemide crosses the placental barrier. It must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

LACTATION

Frusemide passes into breast milk and may inhibit lactation. Women must not breast-feed if they are treated with frusemide.

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

- Metabolism and nutrition disorders
    - 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 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
  - 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
    - 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 frusemide 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, AGEP (acute generalized exanthematous pustulosis) 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
  - 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

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

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

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

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 (including AV 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.

Management
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.

INCOMPATIBILITIES / COMPATIBILITIES

applies only to solutions for injection:
Lasix® must not be mixed with other drugs in the same syringe

applies only to solutions for injection or infusion:
Lasix® must not be infused together with other drugs.

Lasix® is a solution with a pH of about 9 with no buffering capacity. Therefore, the active ingredient may precipitate at pH values below 7. If this solution is diluted, care must therefore be taken to ensure that the pH of the diluted solution is in the weakly alkaline to neutral range.

Normal saline solution is suitable as diluent. It is recommended that diluted solutions be used as soon as possible.

STORAGE CONDITION

Protect from light.

EXPIRY DATE

Do not use later than the date of expiry.
Keep medicine out of reach of children.

PRESENTATION

Tablets of 40 mg

Ampoule of 2ml
Ampoule of 4ml

Marketed by:
Sanofi India Limited, Sanofi House, CT Survey No 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai 400072

Dated: September 2017
Source: CCDS Version 12 dated 23rd June 2017