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

Lasix®
Furosemide
Tablet

Composition
Each tablet contains, as active ingredient, 40 mg furosemide.
Excipients: Maize starch, pregelatinized maize starch, lactose, colloidal anhydrous silica, talc, magnesium stearate.

Properties
Lasix is a medicine which increases urine excretion (loop diuretic) and lowers high blood pressure (antihypertensive).

Indications
- Oedema due to cardiac, hepatic, or renal disorders (in the presence of nephritic syndrome, treatment of the basic disorder is the prime concern). Oedema due to burns. Mild to moderate hypertension.

Posology and method of administration
The dosage should be tailored to individual needs, especially according to the success of therapy. The lowest dose at which the desired effect is obtained should always be used.

For adults, the following dosage guidelines apply:

Oedema *due to cardiac, hepatic,* or *renal disorders*:

The initial dose for adults is 1 Lasix 40 mg tablet (equivalent to 40 mg furosemide). If adequate diuresis is not achieved, the individual dose may be doubled after 6 hours to 2 Lasix 40 mg tablets (equivalent to 80 mg furosemide). If satisfactory diuresis is still not attained, 4 Lasix 40 mg tablets (equivalent to 160 mg furosemide) can be administered after a further 6 hours. If necessary, initial doses of over 200 mg furosemide may be used in exceptional cases under careful clinical supervision.

The daily maintenance dose is usually 1 - 2 Lasix 40 mg tablets (equivalent to 40 – 80 mg furosemide). The weight loss caused by increased diuresis should not exceed 1 kg per day.

In nephrotic syndrome, the dose must be determined carefully because of the risk of increased undesirable effects.

Oedemas due to burns:

The daily and/or single dose can be between 1 and 2 ½ Lasix 40 mg tablets (equivalent to 40 - 100 mg furosemide); in exceptional cases in impaired renal function, up to 6 Lasix 40 mg tablets (equivalent to 240 mg furosemide) may be administered.

Intravascular volume depletion must be corrected before using Lasix 40 mg tablets.

Mild to moderate hypertension:

One Lasix 40 mg tablet (equivalent to 40 mg furosemide) may be taken once daily, alone or in combination with other medicinal products.

Use in children:

Children generally receive 1 (to 2) mg furosemide per kg body weight/day, but at most 40 mg furosemide per day.

Method of administration and duration of use

The tablets should be taken on an empty stomach and swallowed whole with adequate liquid (e.g. 1 glass of water).
The duration of use depends on the nature and severity of the disorder.

Contraindications
Lasix 40 mg tablets must not be used in the following cases:
- hypersensitivity to furosemide, sulfonamides (possible cross sensitivity with furosemide) or to any of the excipients,
- renal failure with anuria refractory to furosemide therapy,
- hepatic coma and precoma associated with hepatic encephalopathy,
- severe hypokalaemia (see section Undesirable effects),
- severe hyponatraemia,
- hypovolaemia or dehydration,
- breastfeeding mothers.

Special warnings and precautions for use
Extra caution should be exercised in the following situations:
- hypotension,
- manifest or latent diabetes mellitus (regular monitoring of blood sugar levels),

- gout (regular monitoring of serum uric acid),
- impaired micturition (e.g. in prostatic hypertrophy, hydronephrosis, ureteral stenosis),
- hypoproteinaemia, e.g. in nephrotic syndrome (careful adjustment of the dose),
- hepatorenal syndrome (rapidly progressing renal insufficiency combined with severe liver disease, e.g. liver cirrhosis),
- patients who would be at particular risk from an unwanted significant drop in blood pressure, e.g. patients with cerebrovascular circulatory disorders or coronary heart disease,
- premature infants (risk of developing nephrocalcinosis/nephrolithiasis; monitoring of renal function, kidney ultrasound).

In premature infants with respiratory distress syndrome, diuretic treatment with furosemide in the first weeks of life can increase the risk of persistence of patent ductus arteriosus.

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

In patients with micturition disorders (e.g. prostatic hypertrophy) furosemide should only be used if provision has been made for free flow of urine since sudden urine production can lead to urinary retention with overextension of the bladder.

Furosemide leads to increased elimination of sodium and chloride and therefore water. Elimination of other electrolytes (particularly potassium, calcium and magnesium) is also increased. Since fluid-electrolyte balance disorders are often observed during treatment with Lasix due to increased electrolyte elimination, serum electrolytes should be monitored regularly.

Especially during long-term therapy with Lasix, serum electrolytes (particularly potassium, sodium, calcium) bicarbonate, creatinine, urea, and uric acid, as well as blood sugar levels should be regularly monitored.

Particularly close monitoring is required in patients with a high risk of developing electrolyte disorders, or in the case of severe fluid depletion (e.g. due to vomiting, diarrhoea or intense sweating). Hypovolaemia or dehydration and pronounced electrolyte disturbances or disruption of the acid-base balance must be corrected. This may require temporary discontinuation of treatment with furosemide.

Possible development of electrolyte disorders is affected by underlying disease (e.g. liver cirrhosis, heart failure), concomitant medication (see Section Interaction with other medicinal products and other forms of interaction) and diet.

The weight loss caused by increased urine excretion should not exceed 1 kg/day irrespective of the extent of urine excretion.

In nephrotic syndrome, the dose must be carefully adjusted because of the risk of increased undesirable effects.

Concomitant use with risperidone:
In placebo-controlled studies with risperidone in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide 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 furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly low-dose thiazide diuretics) 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 before the decision to treat is made. 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 Section Contraindications).
The possibility exists of exacerbation or activation of systemic lupus erythematosus.
Use of Lasix can yield positive results in doping tests. In addition, the abuse of Lasix as a doping agent can endanger health.

Warnings on specific excipients
Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose- galactose malabsorption should not take Lasix 40 mg tablets.

Effects on ability to drive and use machines
As individual reactions may vary, the ability to drive, use machines or work without a secure support may be impaired. This applies particularly at the start of treatment, when doses are increased or treatments are switched, or when the drug is taken with alcohol.

Interaction with other medicinal products and other forms of interaction
The simultaneous use of furosemide and glucocorticoids, carbenoxolone or laxatives can lead to increased potassium depletion with the risk of hypokalaemia. In this respect, large amounts of licorice act like carbenoxolone.
Non-steroidal anti-inflammatory drugs (e.g. indometacin and acetylsalicylic acid) can reduce the effect of furosemide.

In patients who develop hypovolaemia during furosemide therapy, or in those who are dehydrated, the simultaneous administration of non-steroidal anti-inflammatory agents can trigger acute renal failure.
Probenecid, methotrexate and other medicinal products which, like furosemide, are extensively secreted in the renal tubules, can reduce the effect of furosemide.
On concomitant administration with phenytoin, a reduced effect of furosemide has been described.
As sucralfate reduces the uptake of furosemide from the intestine and therefore reduces its effect, an interval of at least 2 hours should be allowed between administration of the two medicinal products.
Aliskiren lowers the plasma concentration of orally administered furosemide. Monitoring of the diuretic effect of furosemide is recommended when initiating and adjusting the dose of concomitant aliskiren therapy.
On concomitant administration with cardiac glycosides, furosemide-related hypokalaemia and/ or hypomagnesaemia increase the sensitivity of the myocardium to cardiac glycosides. There is a greater risk of ventricular arrhythmias (including torsades de pointes) if furosemide is used concomitantly with medicinal products that can cause a prolonged QT interval (e.g. terfenadine, some class I and class III antiarrhythmic agents), and in patients with electrolyte disturbances.
The toxicity of high-dose salicylates can be potentiated when they are administered concomitantly with furosemide.
Furosemide can potentiate the harmful effects of nephrotoxic medicinal products (e.g. antibiotics such as aminoglycosides, cephalosporins, polymyxins).
Deterioration in renal function may be observed in patients who are treated concomitantly with furosemide and high doses of certain cephalosporins.
The ototoxicity of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) and other ototoxic medicinal products can be increased by the simultaneous administration of furosemide. Any hearing disorders that occur may be irreversible. The simultaneous use of the above mentioned medicinal products should therefore be avoided.
If cisplatin and furosemide are administered concomitantly, hearing damage may occur. If forced diuresis with furosemide is attempted during cisplatin treatment, furosemide should only be used at low doses (e.g. 40 mg in patients with normal renal function) and when there is a positive fluid balance. Otherwise, cisplatin nephrotoxicity may be enhanced.
The concomitant administration of furosemide and lithium leads to an increase in the cardiac and neurotoxic effects of lithium via reduced lithium excretion. It is therefore recommended that plasma lithium levels be carefully monitored in patients receiving this combination.
If other antihypertensive agents, diuretics or medicinal products with blood-pressure-lowering potential are used at the same time as furosemide, a greater drop in blood pressure is to be expected. A severe drop in blood pressure or even shock, and a deterioration in renal function (in isolated cases acute renal failure), have been observed, particularly when an ACE inhibitor or angiotensin-II-receptor antagonist were administered for the first time or for the first time in higher doses. If possible, the furosemide therapy should therefore be temporarily discontinued, or the dose at least reduced for three days before treatment with an ACE inhibitor or angiotensin- II-receptor antagonist is started or doses are increased.
Furosemide can reduce the renal elimination of probenecid, methotrexate and other medicinal products which, like furosemide, are extensively secreted in renal tubules. In high-dose treatment (especially with both furosemide and the other medicinal product), this can lead to elevated serum levels and a greater risk of undesirable effects due to furosemide or the concomitant medication. The effect of theophylline or curare-type muscle relaxants may be increased by furosemide.
The effect of antidiabetic agents or hypertensive sympathomimetics (e.g. epinephrine, norepinephrine) may be reduced if furosemide is coadministered.
In patients treated with risperidone, caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide, or with other potent diuretics, should be considered before a decision to treat is made. (See Section Special warnings and precautions for use regarding increased mortality in elderly patients with dementia receiving risperidone concomitantly.) Levothyroxine: High doses of furosemide 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.

Other interactions

The concomitant administration of cyclosporin A and furosemide is associated with an increased risk of gouty arthritis as a result of furosemide-induced hyperuricaemia and impairment of renal uric acid excretion by cyclosporin.
In patients who were at high risk of renal damage due to X-ray contrast media and who were treated with furosemide, a deterioration in renal function occurred more frequently after a contrast examination than in at-risk patients who received only an intravenous supply of fluid (hydration) before the contrast-enhanced examination.
After intravenous administration of furosemide within 24 hours of treatment with chloral hydrate, a feeling of heat, outbreaks of sweating, restlessness, nausea, a rise in blood pressure, and tachycardia may be experienced in isolated cases. The simultaneous use of furosemide and chloral hydrate should therefore be avoided.

Pregnancy and lactation

Pregnancy
Furosemide should only be used in pregnancy for short periods and after the need to treat is carefully weighed as it crosses the placental barrier.
Diuretics are not suitable for the routine treatment of hypertension and oedema in pregnancy, since they impair placental perfusion and thereby intrauterine growth.
However, if furosemide has to be given in maternal heart failure or renal insufficiency, electrolytes and haematocrit as well as the foetal growth must be closely monitored. Displacement of bilirubin from the albumin binding site, resulting in an increased risk of kernicterus in hyperbilirubinaemia, has been described for furosemide.
Furosemide crosses the placental barrier and reaches 100% of maternal serum concentration in cord blood. No malformations in humans that could be associated with exposure to furosemide have been reported to date. There is however insufficient data to provide a conclusive assessment of possible damaging effects on the embryo/foetus. *In utero* foetal urine production may be stimulated. Urolithiasis has been observed in premature infants treated with furosemide.

Breast-feeding
Furosemide is excreted in human milk and inhibits lactation. Women should therefore not be treated with furosemide if they are breast-feeding. If necessary, breast-feeding should be discontinued (also see Section Contraindications).

Undesirable effects
The following categories are used to assess the incidence rates of undesirable effects:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

The incidence rates of adverse effects are based on literature data and refer to studies that included a total of 1,387 patients receiving various doses of furosemide in a number of different indications.

Blood and lymphatic system disorders:
Common: haemoconcentration (through excessive diuresis). Uncommon: thrombocytopenia.
Rare: eosinophilia, leukopaenia.
Very rare: haemolytic anaemia, aplastic anaemia, agranulocytosis.
Signs of agranulocytosis may include fever with shivering, mucous membrane changes and sore throat.

Immune system disorders:
Uncommon: allergic skin and mucous membrane reactions (see "Skin and subcutaneous tissue disorders").
Rare: severe anaphylactic and anaphylactoid reactions such as anaphylactic shock (for treatment, see Section Overdose).
The first signs of shock include skin reactions such as flushing or urticaria, restlessness, headache, sweating, nausea, cyanosis.
Not known: exacerbation or activation of systemic lupus erythematosus.

Metabolism and nutrition disorders (see Section Special warnings and precautions for use):
Very common: electrolyte disorders (including symptomatic manifestations), dehydration and hypovolaemia (particularly in elderly patients), elevated triglycerides.
Common: hyponatraemia and hypochloraemia (particularly in restricted sodium chloride intake), hypokalaemia (particularly in concomitant reduction of potassium intake and/or increased potassium losses, e.g. due to vomiting or chronic diarrhoea); elevated blood cholesterol, elevated blood uric acid and episodes of gout.
Uncommon: reduced glucose tolerance and hyperglycaemia. In patients with manifest diabetes mellitus, this can lead to deterioration of the metabolic state. Latent diabetes mellitus may become manifest (see Section Special warnings and precautions for use).
Not known: hypocalcaemia, hypomagnesaemia, metabolic alkalosis, Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide.
Commonly observed symptoms of sodium deficiency include apathy, calf cramps, loss of appetite, weakness, drowsiness, vomiting and confusion.
Hypokalaemia may manifest as neuromuscular signs (muscle weakness, paraesthesia, paraesis), intestinal signs (vomiting, constipation, meteorism), renal signs (polyuria, polydipsia) and cardiac signs (disorders of impulse formation and conduction). Severe potassium depletion can result in paralytic ileus, consciousness disorders or even coma.

Hypocalcaemia can cause tetany in rare cases.
Tetany or the development of cardiac arrhythmias have been observed in rare cases as a result of hypomagnesaemia.

Nervous system disorders:
Common: hepatic encephalopathy in patients with hepatic insufficiency (see Section Contraindications).
Rare: paraesthesia.
Not known: dizziness, fainting and loss of consciousness, headache.

Ear and labyrinth disorders:
Uncommon: hearing disorders, mostly reversible, particularly in patients with renal insufficiency or hypoproteinaemia (e.g. in nephrotic syndrome) and/or on excessively rapid intravenous injection. Deafness (sometimes irreversible).
Rare: tinnitus.

Vascular disorders:
Very common (on intravenous infusion): hypotension including orthostatic dysregulation (see Section Special warnings and precautions for use).
Rare: vasculitis.
Not known: thrombosis (particularly in elderly patients).
In excessive diuresis, circulatory disorders (even circulatory collapse) may occur, especially in children and elderly patients, and mainly manifest as headaches, dizziness, visual disorders, dry mouth and thirst, hypotension and orthostatic dysregulation.

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

Hepatobiliary disorders:
Very rare: intrahepatic cholestasis, elevated transaminases.

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

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

Renal and urinary disorders:
Very common: elevated blood creatinine. Common: increased urine volume.
Rare: tubulointerstitial nephritis.
Not known: elevated urine sodium, elevated urine chloride, elevated blood urea, symptoms of impaired micturition (e.g. in patients with prostatic hypertrophy, hydronephrosis, ureteral stenosis) to urinary retention with secondary complications (see Section Special warnings and precautions for use), nephrocalcinosis and/or nephrolithiasis in premature infants (see Section Special warnings and precautions for use), renal failure (see Section Interaction with other medicinal products and other forms of interaction).

Congenital, familial and genetic disorders:
Not known: increased risk of persistence of patent ductus arteriosus if premature infants are treated with furosemide in the first weeks of life.

General disorders:
Rare: fever.

Overdose

a) Symptoms of an overdose

The clinical picture in acute or chronic overdose depends on the extent of water and electrolyte loss. Overdose can lead to hypotension, orthostatic dysregulation, electrolyte disturbances (hypokalaemia, hyponatraemia, hypochloraemia) or alkalosis. In more severe fluid depletion, pronounced hypovolaemia, dehydration, circulatory collapse and haemoconcentration with a tendency to thrombosis may occur. In rapid water and electrolyte losses, delirium may be observed. In rare cases, anaphylactic shock (symptoms: sweating, nausea, cyanosis, significant drop in blood pressure, consciousness disorders or even coma) may be observed.

b) Treatment of overdose

In cases of overdose or in patients with signs of hypovolaemia (hypotension, orthostatic dysregulation), treatment with Lasix must be discontinued immediately.
If only a short time has passed since furosemide was taken orally, it is advisable to take steps for the primary elimination of poisoning (induced vomiting, gastric lavage) and absorption-reducing measures (activated charcoal).

In more severe cases, vital signs must be monitored along with repeated assessments of the water and electrolyte balance, acid-base balance, blood sugar levels and substances excreted in urine, and any abnormal levels corrected if necessary.
In patients with impaired micturition (e.g. prostatic hypertrophy) provision must be made for free flow of urine because sudden urine production can lead to urinary retention with overextension of the bladder.
Treatment of hypovolaemia: volume replacement. Treatment of hypokalaemia:
potassium replacement.
Treatment of circulatory collapse: patients should be placed in the shock position, if necessary shock therapy.
Emergency measures in the event of anaphylactic shock:
At the first signs (e.g. skin reactions such as urticaria or flushing, restlessness, headache, outbreaks of sweating, nausea, cyanosis):

- place venous access,
- along with usual emergency measures, place the patient in a supine position with the legs raised, keep the airways clear and give oxygen,
- intensive care emergency measures (including the administration of epinephrine, volume replacement fluids, glucocorticoids).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties Pharmacotherapeutic group: high-ceiling diuretic
ATC code: C03CA01

Furosemide is a potent, short- and fast-acting loop diuretic. By blocking the $Na^+/2Cl^-/K^+$ ion carrier, it inhibits reabsorption of these ions in the ascending limb of the loop of Henle. Fractional sodium excretion can constitute up to 35% of the sodium that has undergone glomerular filtration. Increased sodium excretion leads to greater urine excretion and an increase in K^+ secretion in the distal tubules via osmotically bound water. Excretion of Ca^{2+} and Mg^{2+} ions is also increased. In addition to the depletion of these electrolytes, reduced excretion of uric acid and disruption of the acid-base balance leading to possible metabolic alkalosis may occur.
Furosemide interrupts the tubuloglomerular feedback mechanism in the macula densa so that saluretic efficacy is not attenuated.
Furosemide leads to dose-dependent stimulation of the renin-angiotensin-aldosterone system.
In heart failure, furosemide causes an acute reduction in the preload on the heart by dilating the venous capacitance vessels. This early vascular effect appears to be mediated by prostaglandins and requires adequate renal function with activation of the renin-angiotensin-aldosterone system and intact prostaglandin synthesis.
Furosemide lowers blood pressure as a result of increased sodium chloride excretion and a reduced response of the smooth vascular musculature to vasoconstrictor stimuli, and through decreased blood volume.

Pharmacokinetic properties

Following oral administration, 60 - 70% of the furosemide dose is absorbed in the gastrointestinal tract. In patients with chronic heart failure or nephrotic syndrome, absorption may be reduced to less than 30%.
Onset of action can be expected after about 30 minutes. Peak plasma concentrations are reached approximately 1 hour after intake of the tablets.
Plasma protein binding of furosemide is about 95%. It may be reduced in renal insufficiency by up to 10%. The relative volume of distribution is about 0.2 l/kg body weight (in neonates 0.8 l/ kg body weight).
Furosemide is metabolised in the liver only to a minor extent (about 10%) and is mostly excreted unchanged. Two-thirds is eliminated via the kidneys and one-third via bile and faeces. In normal renal function, the elimination half-life is about 1 hour. It may be prolonged to up to 24 hours in terminal renal failure.

Preclinical safety data

Acute oral toxicity was found to be low in all the studied species. Chronic toxicity studies in rats and dogs gave rise to changes in the kidneys (including fibrosis and calcification).
In vitro and *in vivo* genotoxicity studies with furosemide provided no clinically relevant evidence of genotoxic potential.
Long-term studies in rats and mice showed no evidence of carcinogenic potential.
Following the administration of high doses in reproductive toxicology studies, a reduced number of differentiated glomeruli and skeletal anomalies in the scapula, humerus and ribs (due to hypokalaemia) were observed in rat foetuses, as well as hydronephrosis in mouse and rabbit foetuses.

Storage Conditions

Do not store above 30^{o}C.

Shelf Life

Do no use later than the date of expiry.

Presentation

Blister of 100 tablets.

Manufacturer

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