PRODUCT MONOGRAPH

PrLasix® ORAL SOLUTION
furosemide oral solution Mfr. Std.
Oral solution 10 mg/mL
Diuretic

ATC Code: C03CA01
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LASIX® ORAL SOLUTION
(furosemide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Non-medicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Solution 10 mg/mL</td>
<td>Alcohol, butylated hydroxyanisol, butylated hydroxytoluene, glycerine, methylparaben, natural orange flavour, polysorbate 80, potassium sorbate, purified water, sodium hydroxide and sorbitol.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

LASIX® (furosemide) is indicated for:

- The treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease including, nephrotic syndrome, as well as other edematous states amenable to diuretic therapy.
- Can also be used alone, in the control of mild to moderate hypertension, or in combination with other antihypertensive agents in more severe cases.

Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with LASIX alone.

Pediatrics
When administered to children, LASIX therapy should be instituted in the hospital, in carefully selected patients, under close observation with frequent monitoring of serum electrolytes (see DOSAGE AND ADMINISTRATION section).

The available pediatric data does not allow for a recommendation of a specific age range in this population.

Geriatrics (> 61 years of age)
Use in the geriatric population is associated with differences in safety (see WARNINGS AND PRECAUTIONS).
CONTRAINDICATIONS

LASIX (furosemide) is contraindicated in:

- Patients who are hypersensitive to furosemide, sulfonamide-derived drugs or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.
- Patients with complete renal shutdown. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued.
- Patients with hepatic coma and precoma or in states of electrolyte depletion until the basic condition is improved or corrected. Therapy with LASIX should not be initiated in these patients (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic section).
- Severe hyponatremia, hypokalemia, hypovolemia, dehydration or hypotension must be regarded as contraindications until serum electrolytes and fluid balance and blood pressure have been restored to normal levels (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).
- As furosemide may be capable of displacing bilirubin from albumin at least "in vitro", it should not be administered to jaundiced newborn infants or to infants suffering from diseases (e.g. Rh incompatibility, familial non-hemolytic jaundice, etc.) with the potential of causing hyperbilirubinemia and possibly kernicterus.
- Women must not breast-feed if they are treated with furosemide (see WARNINGS AND PRECAUTIONS section).

WARNINGS AND PRECAUTIONS

General

LASIX (FUROSEMIDE) IS A POTENT DIURETIC WHICH IF GIVEN IN EXCESSIVE AMOUNTS CAN LEAD TO A PROFOUND DIURESIS WITH WATER AND ELECTROLYTE DEPLETION. THEREFORE, CAREFUL MEDICAL SUPERVISION IS REQUIRED, AND DOSE AND DOSE SCHEDULE HAVE TO BE ADJUSTED TO THE INDIVIDUAL PATIENT'S NEEDS (SEE DOSAGE AND ADMINISTRATION).

All patients receiving LASIX therapy should be observed for signs and symptoms of fluid or electrolyte imbalance, hyponatremia, hypochloremic alkalosis, hypovolemia, hypomagnesemia, or hypocalcemia: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oligourea, tachycardia, arrhythmia, or gastro-intestinal disturbances such as nausea and vomiting, increases in blood glucose and alteration in glucose tolerance tests.

During long-term therapy a high-potassium diet is recommended. Potassium supplements may be required especially when high doses are used for prolonged periods. Some electrolyte
disturbances (e.g. hypokalemia, hypomagnesemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome.

Particular caution with potassium levels is necessary when the patient is on digitalis glycosides, potassium-depleting steroids, or in the case of infants and children. Potassium supplementation, diminution in dose, or discontinuation of LASIX therapy may be required.

Since rigid sodium restriction is conducive to both hyponatremia and hypokalemia, strict restriction in sodium intake is not advisable in patients receiving LASIX therapy. Urinary outflow must be secured. Patients with urinary outflow require careful monitoring—especially during the initial stages of treatment (see ADVERSE REACTIONS-Post-Market Adverse Drug Reactions-Renal and urinary disorders section).

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

**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 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 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 (see CONTRAINDICATIONS section) and should therefore be avoided in elderly patients with dementia.

**Carcinogenesis and Mutagenesis**

Carcinogenicity: Furosemide in the approximate amount of 200 mg/kg body weight daily was administered to female mice and rats over a 2-year period with their diet. An increased incidence of mammary adenocarcinoma was noted in the mice, but not in the rats. These tumors occurred with a positive trend, and the incidence in the high dose group was increased compared to the control, in addition, the high-dose rate was about five fold over the historical rate. These tumors are considered to be associated with furosemide administration. This dose is considerably greater than the therapeutic dose administered in human patients.

In a carcinogenicity study, rats were administered furosemide in daily doses of 15 and 30 mg/kg body weight. Male rats in the 15 mg/kg-dose category, but not in the 30 mg/kg-dose category, showed a marginal increase in uncommon tumours.
**Mutagenicity:** In in-vitro tests on bacteria and mammalian cells, both positive and negative results have been obtained. Induction of gene and chromosome mutations, however, has been observed only where furosemide reached cytotoxic concentrations.

**Ear/Nose/Throat**

Cases of tinnitus and reversible deafness have been reported. There have also been some reports of cases, the majority in children undergoing renal transplantation, in which permanent deafness has occurred. In these latter cases, the onset of deafness was usually insidious and gradually progressive up to 6 months after furosemide therapy. Hearing impairment is more likely to occur in patients with hypoproteinemia or severely reduced renal function or in patients who are also receiving drugs known to be ototoxic. Since this may lead to irreversible damage, these drugs must only be used with furosemide if there are compelling medical reasons.

**Endocrine and Metabolism**

Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial blood sugar levels have been observed. Rare cases of precipitation of diabetes mellitus have been reported.

Asymptomatic hyperuricemia can occur and a gout attack may rarely be precipitated.

**Hepatic/Biliary/Pancreatic**

It may be advisable to hospitalize patients with hepatic cirrhosis and ascites prior to initiating therapy. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma, therefore, strict observation is necessary during the period of diuresis.

Supplemental potassium chloride and, if required, an aldosterone antagonist, are helpful in preventing hypokalemia and metabolic alkalosis (see CONTRAINDICATIONS section). Particularly careful monitoring is necessary in patients with hepatorenal syndrome.

**Peri-Operative Considerations**

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with LASIX and it is advisable to discontinue LASIX for one week prior to any elective surgery.

**Special Populations**

**Pregnant Women**

The teratogenic and embryotoxic potential of furosemide in humans is unknown. The drug should not be used in pregnant women or in women of childbearing potential unless in the opinion of the attending physician the benefits to the patient outweigh the possible risk to the foetus.
Reproductive and teratological studies have been performed in mice, rats, rabbits, cats, dogs and monkeys. With the exception of mice and rabbits, no abnormalities attributed to furosemide were detected. Furosemide caused unexplained maternal deaths and abortions in the rabbit at a daily dose of 50 mg/kg (approximately three times the maximum recommended human daily dose of 1000 mg orally) when administered between days 12 to 17 of gestation. In another study in rabbits, a dose of 25 mg/kg caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate foetal lethality which can precede maternal deaths.

The results of a mouse study and one of the three rabbit studies also showed an increased incidence of distention of the renal pelvis and, in some cases, of the ureters in foetuses derived from treated dams as compared to the incidence of foetuses from the control group.

Treatment during pregnancy requires monitoring of fetal growth.

**Nursing Women**

It should be noted that diuretics may partially inhibit lactation and that LASIX passes into the breast milk. Women must not breast-feed if they are treated with furosemide (see CONTRAINDICATIONS section).

**Pediatrics**

LASIX may lower serum calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

In premature infants LASIX may precipitate nephrocalcinosis/nephrolithiasis. When administered to premature infants with respiratory distress syndrome in the first few weeks of life, diuretic treatment with LASIX may accentuate the risk of a patent ductus arteriosus (see WARNINGS AND PRECAUTIONS- Monitoring and Laboratory Tests section).

Caution is required in neonates because of prolonged half-life of furosemide.

**Geriatrics (> 61 years of age)**

Excessive diuresis induced by LASIX may result in dehydration and reduction of blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism particularly in elderly patients. LASIX may cause electrolyte depletion.

Furosemide binding to albumin may be reduced in elderly patients.

The drug is known to be substantially excreted unchanged by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal functions, care should be taken in dose selection and may be useful to monitor renal function.

In general dose selection for the elderly patients should be cautious, usually starting at the low end of dosage range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and the concomitant disease or other drug therapy.
Monitoring and Laboratory Tests

Frequent serum electrolyte, creatinine and CO2 content determinations should be performed during the first few months of therapy and periodically thereafter. It is essential to replace electrolyte losses and to maintain fluid balance so as to avoid any risk of electrolyte depletion (hyponatremia, hypochloremia, hypokalemia, hypomagnesemia or hypocalcemia), hypovolemia, or hypotension.

Checks on urine and blood glucose should be made at regular intervals especially in diabetics and in those suspected of latent diabetes when receiving LASIX. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial blood sugar levels have been observed.

Frequent BUN determinations during the first few months of therapy and periodically thereafter, as well as regular observations for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions are advisable.

Particularly careful monitoring is necessary in:
- patients with hypoproteinemia. Cautious dose titration is required.
- premature infants. Renal function must be monitored and renal ultrasonography performed.
- patients with hypotension
- 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).
- patients with hepatorenal syndrome.
- patients with latent and manifest diabetes mellitus
- patients with gout

Occupational Hazards

LASIX may lower the state of patient alertness and/or reactivity particularly at the start of treatment as a result of a reduction in blood pressure and of other adverse reactions (see ADVERSE REACTIONS section).
ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions
No data available.

Post-Market Adverse Drug Reactions
Adverse reactions are categorized below by body system.

Blood and lymphatic system disorders
Anemia, eosinophilia, leukopenia and thrombocytopenia (with purpura) have occurred, as well as agranulocytosis, aplastic anemia and hemolytic anemia.

Ear and Labyrinth disorders
Cases of tinnitus and sometimes irreversible deafness have been reported. There have also been some reports of cases, the majority in children undergoing renal transplantation, in which permanent deafness has occurred. In these latter cases, the onset of deafness is usually insidious and gradually progressive up to 6 months after furosemide therapy. Hearing disorder is more likely to occur in patients with hypoproteinemia or severely reduced renal function who are also receiving drugs known to be ototoxic.

Vertigo has been reported.

Eye disorders
Xanthopsia and blurred vision have been reported.

Gastrointestinal disorders
Acute pancreatitis, oral and gastric burning, diarrhea, nausea, vomiting and constipation have been reported. Rare occurrence of sweet taste has been reported.

Hepatobiliary disorders
Jaundice (intrahepatic cholestatic jaundice) and cholestasis have been reported.

Immune system disorders
Hypersensitivity reactions to furosemide also include photosensitivity, paresthesia and fever. Systemic hypersensitivity reactions include vasculitis and necrotizing angiitis. Severe anaphylactic or anaphylactoid reactions (e.g. with shock) occur rarely. Exacerbation or activation of systemic lupus erythematosus.

Investigations
Increase in liver transaminases has been reported. Transient elevations of BUN have been observed, especially in patients with renal insufficiency.
As with other diuretics, there may be an increase in serum creatinine, uric acid (this may lead to gout attack in predisposed patients), blood urea, cholesterol and triglyceride levels during furosemide treatment.

**Metabolism and nutrition disorders**

Electrolyte depletion has occurred during therapy with LASIX, especially in patients receiving higher doses with a restricted salt intake. Electrolyte depletion (hyponatremia, hypochloremia, hypokalemia, hypocalcemia and hypomagnesemia) manifests itself by adverse reactions attributed to various body systems: weakness, dizziness, drowsiness, polyuria, polydipsia, orthostatic hypotension, lethargy, sweating, bladder spasms, anorexia, vomiting, mental confusion, meteorism, thirst, headache, muscle cramp, muscle weakness, tetany and disorder of cardiac rhythm (see WARNINGS AND PRECAUTIONS section).

The development of electrolyte disturbances (including symptomatic) is influenced by factors such as underlying diseases (e.g. liver cirrhosis, cardiac failure), concomitant medication and nutrition.

Cases of Pseudo-Bartter syndrome (hypochloremia, hypokalemia, alkalosis, normal to low blood pressures, and elevated plasma renin and aldosterone) have been reported in the context of misuse and/or long-term use of furosemide.

Treatment with LASIX has occasionally caused some deterioration of metabolic control in cases of manifest diabetes, or has made latent diabetes manifest. Metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or, e.g. where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses.

Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated. In extreme cases, hypovolemia may lead to dehydration, circulatory collapse, hemoconcentration and thrombophilia. Thrombophlebitis and emboli have been reported.

**Musculoskeletal and connective tissue disorders:**

Cases of rhabdomyolysis have been reported, often in the context of severe hypokalemia.

**Nervous system disorders**

At the commencement of treatment, excessive diuresis may give rise, especially in elderly patients, to a feeling of pressure in the head, dizziness, headache fainting or loss of consciousness.

Paresthesia has been reported.

Hepatic encephalopathy in patients with hepatocellular insufficiency has been reported.
Renal and urinary disorders

Symptoms of obstructed micturition (e.g. in hydronephrosis, prostatic hypertrophy, ureterostenosis) may become manifest or may be aggravated during medication with diuretics.

Interstitial nephritis has been reported.

Increased production of urine may provoke or aggravate complaints in patients with an obstruction of urinary outflow. Thus, acute retention of urine with possible secondary complications may occur. Increases in urine sodium and chloride have also been reported.

There have been some reported cases of renal failure.

In premature infants LASIX may precipitate nephrocalcinosis/nephrolithiasis.

Skin and subcutaneous tissue disorders

Various forms of dermatitis (e.g. dermatitis bullous), including urticaria, erythema multiforme, pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pruritus, epidermolysis bullosa, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have occurred.

Dermatologic reactions to furosemide also include purpura and rash.

Vascular disorders

Too vigorous diuresis may induce orthostatic hypotension or acute hypotensive episodes, which may cause signs and symptoms such as impairment of concentration and reactions, lightheadedness or orthostatic intolerance. There have been some reported cases of thrombosis.

When administered to premature infants with respiratory distress syndrome in the first few weeks of life, diuretic treatment with LASIX may accentuate the risk of a patent ductus arteriosus.

DRUG INTERACTIONS

Overview

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine or curare-type muscle relaxants (see WARNINGS AND PRECAUTIONS – Peri-Operative Considerations section).

In case of concomitant abuse of laxatives, the risk of an increased potassium loss should be considered.

Glucocorticoids, carbenoxolone and licorice may also increase potassium loss.

Administration of LASIX to diabetic patients may result in possible decrease of diabetic control.

Dosage adjustments of the anti-diabetic agent may be needed.
Hearing impairment is more likely to occur in patients who are also receiving drugs known to be ototoxic (e.g. aminoglycosides antibiotics, ethacrynic acid and cisplatin) (see WARNINGS AND PRECAUTIONS section).

In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when LASIX is administered, since LASIX potentiates their hypotensive effect.

Non-steroidal anti-inflammatory drugs (e.g. indomethacin, acetyl-salicylic acid) may attenuate the effect of LASIX and may cause renal failure in case of pre-existing hypovolemia.

Drug-Drug Interactions

The drug interactions discussed in this section are based on either drug interaction case reports, or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Established or Predicted Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Ref</th>
<th>Effect</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>T</td>
<td>↓ furosemide diuretic effect</td>
<td>Anticonvulsants drugs (phenytoin, carbamazepine, phenobarbital), which, like furosemide, undergo significant renal tubular secretion, may also attenuate the effect of furosemide.</td>
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<tr>
<td>Phenobarbital</td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>T</td>
<td>↓ antidiabetic drug effect</td>
<td>The effects of antidiabetic drugs may be reduced.</td>
</tr>
<tr>
<td>Antihypertensive Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>CT</td>
<td>↓ blood pressure and renal function</td>
<td>Especially in combination with ACE inhibitors, a marked hypotension may be seen sometimes progressing to shock. The concomitant administration of LASIX with ACE-inhibitors may lead to deterioration in renal function and, in isolated cases, to acute renal failure. Consideration must be given to interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an ACE inhibitor.</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>CT</td>
<td>↓ blood pressure and renal function</td>
<td>Especially in combination with angiotensin II receptor antagonists, a marked hypotension may be seen sometimes progressing to shock. The concomitant administration of LASIX with angiotensin II receptor antagonists may lead to deterioration in renal function and, in isolated cases, to acute renal failure. Consideration must be given to interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three days before starting treatment with, or increasing the dose of, an angiotensin II receptor antagonist.</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
<td>↓ renal function</td>
<td>Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.</td>
</tr>
<tr>
<td>Proper Name</td>
<td>Ref</td>
<td>Effect</td>
<td>Clinical Comments</td>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chloral Hydrate</td>
<td>C</td>
<td>—</td>
<td>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.</td>
</tr>
<tr>
<td>Chlorothiazides</td>
<td>T</td>
<td>—</td>
<td>The concurrent use of LASIX with chlorothiazide has been reported to decrease hypercalciumia and to dissolve some calculi.</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>T</td>
<td>↑ nephrotoxicity↑ ototoxicity</td>
<td>Nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment. There is also a risk of ototoxic effects if cisplatin and furosemide are given concomitantly.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>CT</td>
<td>—</td>
<td>Concomitant use of cyclosporine A and furosemide is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperuricemia and cyclosporine impairment of renal urate excretion.</td>
</tr>
<tr>
<td>Digitalis Glycosides</td>
<td>T</td>
<td>↓ potassium plasma concentration</td>
<td>Some electrolyte disturbances (e.g. hypokalemia, hypomagnesemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome). Particular caution with potassium levels is necessary when the patient is on digitalis glycosides. Potassium supplementation, diminution in dose, or discontinuation of LASIX therapy may be required (see WARNINGS AND PRECAUTIONS).</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>C</td>
<td>↑ then ↓ thyroid hormones</td>
<td>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.</td>
</tr>
<tr>
<td>Lithium</td>
<td>T</td>
<td>↑ lithium plasma concentration</td>
<td>Renal clearance of lithium is decreased in patients receiving LASIX, resulting in increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels be carefully monitored in patients receiving this combination.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>T</td>
<td>↓ furosemide diuretic effect</td>
<td>Methotrexate, which like furosemide, undergoes significant renal tubular secretion, may also attenuate the effect of furosemide.</td>
</tr>
<tr>
<td>Nephrotoxic Drugs</td>
<td>T</td>
<td>↑ nephrotoxicity</td>
<td>The harmful effects of nephrotoxic drugs on the kidney may be increased.</td>
</tr>
<tr>
<td>Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)</td>
<td>CT</td>
<td>↓ furosemide diuretic effect</td>
<td>Clinical studies have shown that the administration of indomethacin can reduce the natriuretic and anti-hypertensive effect of LASIX in some patients. This response has been</td>
</tr>
</tbody>
</table>
attributed to inhibition of prostaglandin synthesis by indomethacin. Therefore, when indomethacin is added to the treatment of a patient receiving LASIX, or LASIX is added to the treatment of a patient receiving indomethacin, the patient should be closely observed to determine if the desired effect of LASIX is obtained. Indomethacin blocks the LASIX-induced increase in plasma-renin activity. This fact should be kept in mind when evaluating plasma-renin activity in hypertensive patients.

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Ref</th>
<th>Effect</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potassium-depleting Steroids</strong></td>
<td></td>
<td></td>
<td>Some electrolyte disturbances (e.g. hypokalemia, hypomagnesemia) may increase the toxicity of certain other drugs (e.g. digitalis preparations and drugs inducing QT interval prolongation syndrome). Particular caution with potassium levels is necessary when the patient is on potassium-depleting steroids. Potassium supplementation, diminution in dose, or discontinuation of LASIX therapy may be required (see WARNINGS AND PRECAUTIONS).</td>
</tr>
<tr>
<td>Potassium-depleting Steroids</td>
<td>T</td>
<td>↓ potassium plasma concentration</td>
<td></td>
</tr>
<tr>
<td><strong>Probenecid</strong></td>
<td></td>
<td></td>
<td>Probenecid, which like furosemide, undergoes significant renal tubular secretion, may also attenuate the effect of furosemide.</td>
</tr>
<tr>
<td>Probenecid</td>
<td>T</td>
<td>↓ furosemide diuretic effect</td>
<td></td>
</tr>
<tr>
<td><strong>Radiocontrast Agents</strong></td>
<td></td>
<td></td>
<td>Patients who were at high risk for radiocontrast nephropathy treated with furosemide 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.</td>
</tr>
<tr>
<td>Radiocontrast Agents</td>
<td>CT</td>
<td>↑ radiocontrast nephropathy</td>
<td></td>
</tr>
<tr>
<td><strong>Risperidone</strong></td>
<td></td>
<td></td>
<td>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 prior to the decision to use. See PRECAUTIONS section, regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CT</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Salicylates</strong></td>
<td></td>
<td></td>
<td>Patients receiving high doses of salicylates in conjunction with LASIX may experience salicylate toxicity at lower doses because of competition for renal excretory sites.</td>
</tr>
<tr>
<td>Salicylates</td>
<td>T</td>
<td>↑ salicylate toxicity</td>
<td></td>
</tr>
<tr>
<td><strong>Sucralfate</strong></td>
<td></td>
<td></td>
<td>Concurrent administration of LASIX and sucralfate should be avoided, as sucralfate reduces the absorption of furosemide from the intestine and hence weakens its effect.</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>T</td>
<td>↓ furosemide absorption</td>
<td></td>
</tr>
<tr>
<td><strong>Theophylline</strong></td>
<td></td>
<td></td>
<td>The effects of theophylline may be increased.</td>
</tr>
<tr>
<td>Theophylline</td>
<td>T</td>
<td>↑ theophylline effect</td>
<td></td>
</tr>
</tbody>
</table>

Legend: C= Case Study; CT= Clinical Trial; T= Theoretical

Interactions with other drugs have not been established.
**Drug-Food Interactions**
Interactions with food have not been established.

**Drug-Herb Interactions**
Interactions with herbal product have not been established.

**Drug-Laboratory Interactions**
Interactions with laboratory tests have not been established.

**DOSAGE AND ADMINISTRATION**

**Dosing Considerations**
Careful observations for changes in blood pressure must be made when LASIX is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50% as soon as LASIX is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of LASIX, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

**Recommended Dose and Dosage Adjustment**

**Adults (oral)**

**Edema**
The usual initial dose of LASIX is 40 to 80 mg. Ordinarily a prompt diuresis ensues and the starting dose can then be maintained or even reduced. If a satisfactory diuresis has not occurred within 6 hours, succeeding doses should be increased by increments of 20 to 40 mg, if necessary.

Maximum daily dose: 200 mg. Once the effective single dose has been determined, it may be repeated 1 to 3 times a day.

The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which LASIX is given for 2 to 4 consecutive days each week. With doses exceeding 120 mg/day, careful clinical and laboratory observations are particularly advisable.

**Hypertension**

A dosage schedule of 20 to 40 mg twice daily is recommended. Individualized therapy is of great importance. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other antihypertensive agents, rather than to increase the dose of LASIX.
**Pediatrics (oral)**

LASIX therapy should be instituted in the hospital, in carefully selected patients, under close observation with frequent monitoring of serum electrolytes.

Orally, the initial dose should be in the range of 0.5 to 1.0 mg/kg body weight.

The total daily dose (given in divided doses of 6 to 12 hours apart) should not exceed 2 mg/kg orally. In the newborn and in pre mature babies, the daily dose should not exceed 1 mg/kg.

An intermittent dosage schedule should be adopted as soon as possible using the minimum effective dose at the longest possible intervals. Particular caution with regard to potassium levels is always desirable when LASIX is used in infants and children.

**OVERDOSAGE**

**Symptoms**

Dehydration, electrolyte depletion and hypotension may be caused by overdosage or accidental ingestion. In cirrhotic patients, overdosage might precipitate hepatic coma.

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. hypovolemic, dehydration, hemoconcentration, 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.

**Treatment**

The drug should be discontinued and appropriate corrective treatment applied: replacement of excessive fluid and electrolyte losses; serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy).

No specific antidote to furosemide 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).

For management of a suspected drug overdose, contact your regional Poison Control Centre.
ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Animal experiments using stop-flow and micropuncture techniques have demonstrated that LASIX inhibits sodium reabsorption in the ascending limb of Henle's loop as well as in both proximal and distal tubules. The action of LASIX on the distal tubule is independent of any inhibitory effect on carbonic anhydrase or aldosterone. LASIX may promote diuresis in cases which have previously proved resistant to other diuretics.

Pharmacodynamics

A continuous infusion of furosemide is more effective than repetitive bolus injections. Moreover, above a certain bolus dose of the drug there is no significant increase in effect. The effect of furosemide is reduced if there is lowered tubular secretion or intra-tubular albumin binding of the drug.

Pharmacokinetics

Absorption
In man, LASIX is rapidly absorbed from the gastro-intestinal tract. The diuretic effect of furosemide is apparent within one hour following oral administration and the peak effect occurs in the first or second hour. The duration of action is 4-6 hours but may continue up to 8 hours. Following intravenous administration of the drug, the diuresis occurs within 30 minutes and the duration of action is about 2 hours.

Metabolism
A small fraction is metabolized by cleavage of the side chain.

Excretion
Urinary excretion is accomplished both by glomerular filtration and proximal tubular secretion, together this accounts for roughly only 2/3 of the ingested dose, the remainder being excreted in the feces.

The following table summarizes the elimination kinetics of furosemide.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Route of Administration</th>
<th>Dose (mg)</th>
<th>Rate of Administration</th>
<th>Biliary Excretion</th>
<th>Max. Serum Concentration (µg/mL)</th>
<th>t½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Oral</td>
<td>40</td>
<td>—</td>
<td>10-15%</td>
<td>&lt; 1 µg/mL</td>
<td>4.0</td>
</tr>
<tr>
<td>Normal</td>
<td>I.V.</td>
<td>40</td>
<td>Bolus</td>
<td>10-15%</td>
<td>2.5 µg/mL</td>
<td>4.5</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>I.V.</td>
<td>1000</td>
<td>25 mg/min.</td>
<td>60%</td>
<td>53 µg/mL</td>
<td>13.5</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>I.V.</td>
<td>1000</td>
<td>4 mg/min.</td>
<td>—</td>
<td>29 µg/mL</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 1 - Summary of furosemide’s elimination kinetics.
Special Populations and Conditions

**Pediatrics:** Depending on the maturity of the kidney, the elimination of furosemide may be slowed down. The metabolism of the drug is also reduced if the infant’s glucuronisation capacity is impaired.

The terminal half-life is below 12 hours in infants with a post-conceptional age of more than 33 weeks.

In infants of 2 months and older, the terminal clearance is the same as in adults.

**Geriatrics:** The elimination of furosemide is slowed down due to reduced renal function in the elderly.

**Gender:** Data unavailable.

**Race:** Data unavailable.

**Hepatic Insufficiency:** In liver failure, the half-life of furosemide is increased by 30% to 90% mainly due to a larger volume of distribution. Additionally, in this patient group there is a wide variation in all pharmacokinetic parameters.

**Renal Insufficiency:** In renal failure, the elimination furosemide is slowed down and the half-life prolonged; the terminal half-life may be up to 24 hours in patients with severe renal failure. In nephrotic syndrome the reduced plasma protein concentration leads to a higher concentration of unbound (free) furosemide. On the other hand, efficacy of furosemide is reduced in these patients due to binding to intratubular albumin and lowered tubular secretion.

Furosemide is poorly dialyzable in patients undergoing hemodialysis, peritoneal dialysis and CAPD.

**Genetic Polymorphism:** Data unavailable.

**STORAGE AND STABILITY**

**Temperature**
Oral solution: Store between 15° and 30°C. Protect from light.
DOSAGE FORMS, COMPOSITION AND PACKAGING

Lasix solution
Clear, slightly yellowish liquid, with an orange odour, containing 10 mg/mL furosemide.

Available in bottles of 120 mL.

Non-medicinal ingredients: alcohol, butylated hydroxyanisol, butylated hydroxytoluene, glycerine, methylparaben, natural orange flavour, polysorbate 80, potassium sorbate, purified water, sodium hydroxide and sorbitol.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: furosemide
Chemical name: 4-chloro-N-furfuryl-5-sulfamoyl-anthranilic acid
Molecular formula: C₁₂H₁₁ClN₂O₅S
Molecular mass: 330.8

Structural formula:

Physicochemical properties: White to slightly yellow, crystalline powder. Practically insoluble in water; freely soluble in acetone, in dimethylformamide, and in solutions of alkali hydroxides; soluble in methanol; sparingly soluble in alcohol; slightly soluble in ether; very slightly soluble in chloroform, melting at about 210°C (with decomposition).

CLINICAL TRIALS

No data available.

DETAILED PHARMACOLOGY

LASIX (furosemide) has no significant pharmacological effects other than on the renal function.

Renal Pharmacology

In dogs, furosemide demonstrated diuretic properties. Diuresis and sodium excretion were induced by doses of 0.125 mg/kg administered intravenously or 0.5 mg administered orally.

Maximum water and sodium excretion is obtained by oral and intravenous doses of 12.5 and 25 mg/kg respectively. Increased potassium excretion can only be demonstrated with doses exceeding 1 mg/kg. The onset of action is rapid after intravenous and oral administration and the duration of activity is approximately 2 and 4 hours respectively.
Furosemide produces an immediate diuresis after intravenous administration and is effective unilaterally after injection into a renal artery. Its action, therefore, is directly on the kidney. The diuretic response is prompt and relatively brief. At the peak of diuretic response 30-40% of filtered sodium load may be excreted, along with some potassium and with chloride as the major anion. Furosemide augments the potassium output as a result of increased distal potassium secretion. Its diuretic action is independent of changes in acid-base balance. Under conditions of acidosis or alkalosis the diuretic produces chloruresis without augmentation of bicarbonate excretion. It does not inhibit carbonic anhydrase.

On the basis of changes in free-water production furosemide inhibits sodium reabsorption in the ascending limb of Helves loop. However, proximal sites of action are also involved, as determined by micropuncture. Partial distal inhibition of sodium reabsorption is also possible. It also decreases the urinary excretion of uric acid and prolonged administration may lead to hyperuricemia. Since urate is transported in the proximal tubule, the effect of the drug on uric acid excretion further suggests a proximal tubule site of action.

Administration of furosemide may induce extracellular metabolic alkalosis, primarily by virtue of the disproportionate loss of chloride, but also, in part, as a result of the variable depletion of potassium.

**TOXICOLOGY**

The acute toxicity of furosemide has been determined in four animal species:

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>ORAL</th>
<th>INTRAVENOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>1000</td>
<td>300</td>
</tr>
<tr>
<td>Adult Rats</td>
<td>4600</td>
<td>700</td>
</tr>
<tr>
<td>Newborn Rats</td>
<td>400</td>
<td>-</td>
</tr>
<tr>
<td>Rabbits</td>
<td>700</td>
<td>400</td>
</tr>
<tr>
<td>Dogs</td>
<td>2000</td>
<td>over 400</td>
</tr>
</tbody>
</table>

The acute toxicity was characterized by signs of vasomotor collapse, sometimes accompanied by slight convulsions. Surviving animals often became dehydrated and depleted of electrolytes. In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.
Chronic toxicity studies with furosemide were done in rats, dogs and monkeys.

1. **Rats:** A one-year study was performed on one hundred albino rats at dosages of 0, 50, 100, 200 and 400 mg/kg/day orally. Seventy-six rats survived for one year. Ten rats from the two highest dose groups died within the first 10 days of therapy. Histological examination of those animals dying early revealed striking basophilic degeneration of the myocardial fibres with infiltration and necrotic foci consistent with severe electrolyte imbalance.

   In the kidney, the most consistent pathological changes seen were degenerative changes in the tubular epithelium manifested by swollen cells with increased density of the cytoplasm. Occasionally, focal necrosis of the epithelium and decreased cell size were evident, plus accumulation of some calcified material. These changes were considered consistent with the nephropathy of potassium deficiency.

2. **Dogs:** In a six-month study, eighteen out of twenty beagle dogs survived oral daily doses of 0, 10, 30, 100 and 350 mg/kg. The most consistent pathological findings were renal lesions consisting of calcifications and scarring of the renal parenchyma at all doses above 10 mg/kg. The renal capsule above these lesions sometimes showed strikingly enlarged lymph vessels with thickened walls.

3. **Rhesus Monkeys:** In a 12-month study, daily oral doses of furosemide of 27 mg/kg and 60 mg/kg brought about pathological findings that consisted of dilated convoluted tubules with casts in 3 out of 20 animals given 27 mg/kg and in 6 out of 9 animals given 60 mg/kg. These lesions were considered drug related.

**Reproductive and teratological studies**

Reproductive and teratological studies have been performed in mice, rats, rabbits, cats, dogs and monkeys. With the exception of mice and rabbits, no abnormalities attributed to furosemide were detected. Furosemide caused unexplained maternal deaths and abortions in the rabbit at a daily dose of 50 mg/kg (approximately three times the maximum recommended human daily dose of 1000 mg orally) when administered between days 12 to 17 of gestation. In another study in rabbits, a dose of 25 mg/kg caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate foetal lethality which can precede maternal deaths.

The results of a mouse study and one of the three rabbit studies also showed an increased incidence of distention of the renal pelvis and, in some cases, of the ureters in foetuses derived from treated dams as compared to the incidence of foetuses from the control group.
REFERENCES


PART III: CONSUMER INFORMATION  
\textit{Lasix® ORAL SOLUTION}  
(furosemide solution Mfr. Std.)  

This leaflet is part III of a three-part "Product Monograph" published for \textit{Lasix®} in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about \textit{Lasix}. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

\textit{Lasix} has been prescribed to you by your health provider to treat your edema (water retention) or hypertension (high blood pressure).

What it does:

\textit{Lasix} belongs to a group of medicines known as diuretic drugs which improve the elimination of water and salts (electrolytes) in the urine.

When it should not be used:

Do not use \textit{Lasix} if you are allergic to it or to any of the components of its formulation (for list of components see the section on "What the nonmedicinal ingredients are"), or to any sulfonamide-derived drugs. Ask your physician or pharmacist if you are not sure what sulfonamide-derived drugs are.

WARNINGS AND PRECAUTIONS

\textit{Lasix} is a very strong water pill which if given in excessive amounts can lead to a profound water and electrolyte loss from the body. Therefore, careful medical supervision is required. The dose and dose schedule have to be adjusted to the individual patient’s needs.

Before you use \textit{Lasix} talk to your health provider if:

- You have decreased blood pressure.
- You have liver disease or disorder.
- You have kidney disease or disorder.
- It is suspected you might be diabetic (high blood sugar).
- You have decreased ability to pass urine.
- You had an organ transplant.
- You have gout.
- You have lupus or had an episode of lupus.
- You have been told by the doctor that you suffer from a narrowing of the arteries that supply your heart or brain.
- You have recently suffered from excess vomiting or diarrhea.
- You intend to have a surgery and general anesthesia (even at the dentist’s office), as there may be a sudden fall in blood pressure associated with general anesthesia.
- You are breastfeeding. Lasix is passed to the infant during breastfeeding. Do not breastfeed if you intend to take \textit{Lasix}.
- You are pregnant, or think you might be pregnant.
- You intend to change your eating habits.
• You are less than 18 years old.
• You are older than 61 years old.

When administered to children, LASIX therapy should be started in the hospital, in carefully selected patients, under close observation with frequent blood tests to measure electrolytes such as sodium, potassium, chloride, magnesium and calcium.

For elderly patients, (over 61 years old), the dose selection should be cautious, usually starting at the low end of dosage range, reflecting the greater frequency of decreased liver, kidney or heart function.

Studies in elderly patients with dementia have shown that taking LASIX with risperidone is associated with a higher rate of death.

The administration of LASIX to diabetic patients may result in possible decrease of diabetic control.

Dosage adjustments of the antidiabetic agent may be needed.

There have been cases of ringing in the ears, reversible and non-reversible deafness especially in children. This is most true when the patient has severe kidney disease or is taking drugs that are known to sometimes damage the ears while they are taking LASIX. Your doctor will decide if LASIX is the right medication for you/your child based on your particular condition.

LASIX should not be used in pregnant women or in women of childbearing potential unless in the opinion of the attending physician the benefits to the patient outweigh the possible risk to the foetus. Treatment during pregnancy requires monitoring of fetal growth by your doctor.

If you are suffering from hyperuricemia (high uric acid levels in your blood), taking LASIX can sometimes make a gout attack more likely.

Almost all patients can drive or operate machinery while taking LASIX, but you should not perform these tasks, which may require attention, until you know how you tolerate your medicine.

INTERACTIONS WITH THIS MEDICATION

Before using LASIX, tell your health provider about medication you are currently taking. This way appropriate adjustment and decision can be taken for your treatment with LASIX.

Below are drugs or drug classes that may interact with LASIX. These include:
• Drugs to reduce blood pressure (eg. ACE inhibitors, angiotensin II receptor antagonist).
• Diuretics (waterpills), including ethacrynic acid
• Pressor amines such as epinephrine (a medication used to treat life-threatening allergic reactions).
• Medication to treat diabetes, including insulin. The administration of LASIX to diabetic patients may result in possible decrease of diabetic control. Dosage adjustments of the antidiabetic agent may be needed.
• Theophylline, a medication used to treat asthma, chronic bronchitis, and other lung diseases.
• Cisplatin (anti-cancer drug)
• Probenecid (medicine used to treat gout).
• Antibiotics (e.g cephalosporins, aminoglycosides)
• Certain pain and anti-inflammatory drugs (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], acetyl-salicylic acid, indomethacin)
• Drugs used in the treatment of rheumatoid arthritis (methotrexate, cyclosporin).
• Drugs used to treat epilepsy (e.g. phenytoin, carbamazepine, phenobarbital).
• Risperdal, a drug used to treat dementia.
• Lithium (medicine used to treat bipolar depression).
• Sucralfate (antacid drug)
• Sedatives such as phenobarbital or chloral hydrate
• Stimulant laxatives and drugs which may induce low potassium levels (hypokalemia) such as glucocorticoids, and medicine derived from licorice (e.g. carbenoxolone).
• Drugs known to be harmful to the ear (ototoxic) as for instance aminoglycosides antibiotics, ethacrynic acid (a “water pill”) and cisplatin (a drug used to treat some types of cancer).
• Drugs known to be harmful to the kidney.
• Substances used during certain radiological investigations (radiocontrast agents).
• Digitalis (digoxin)
• Certain steroids
• Levothyroxine, a drug used to adjust your thyroid hormone levels
**PROPER USE OF THIS MEDICATION**

During long-term therapy a high-potassium diet may be recommended. You should not be on a strict salt restricted diet. Potassium supplements may be required. Your doctor will monitor your blood tests for blood sugar, potassium and other electrolytes and to monitor liver and kidney function. This is especially important if you have other medical conditions such as diabetes, take other medications or the patient is an infant or child.

**Usual dose:**

Adults (oral) for edema and high blood pressure:

It is important that you take LASIX as prescribed by your doctor.

Usually your doctor will prescribe LASIX at a dose of 20 to 80 mg per day, which you could take as single or 2-3 divided doses, based on the type of administration your physician considers to be the most appropriate for your condition.

Maximum daily dose: 200 mg.

When prescribed to children, LASIX is usually administered in the form of a solution and at a dose that will be determined by the health care provider.

The oral solution should be taken on an empty stomach.

You should always respect the prescribed interval between the doses. Never change the dose of LASIX you are taking unless your doctor tells you to.

This drug is specifically prescribed for you or a child in your care. Do not give it to others, even if they have the same symptoms, and you yourself must not use it for any condition than the one for which it was prescribed.

**Pediatrics (oral):**

LASIX therapy should be instituted in the hospital, in carefully selected patients, under close observation with frequent monitoring of blood tests including electrolytes. The doctor will decide what the best dose for each child.

Orally, the initial dose should be in the range of 0.5 to 1.0 mg/kg body weight.

The total daily dose (given in divided doses of 6 to 12 hours apart) should not exceed 2 mg/kg orally. In the newborn and in premature babies, the daily dose should not exceed 1 mg/kg.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Along with its beneficial effects, LASIX like all other drugs may sometimes cause undesirable effects.

These may include: blurring of vision, constipation, diarrhea, dizziness, dry mouth, fatigue, tachycardia, arrhythmia (heart rhythm disturbance), feeling of pressure in the head, increase in the amount and frequency of your urine, leg cramps, mental confusion, nausea, sweating, thirst, vomiting, hepatic encephalopathy (altered mental state due to liver disease). Talk to your doctor or pharmacist if you experience any of the above.

Stop taking LASIX and contact your doctor immediately if you experience an allergic reaction or any severe side effect.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist immediately</th>
<th>Stop taking drug and seek immediate emergency medical attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing problems; deafness, sometimes non-reversible</td>
<td>Only if severe</td>
<td>✓</td>
</tr>
<tr>
<td>Fever, sore throat, fatigue, lesions in the mouth or on the lips</td>
<td>In all cases</td>
<td>✓</td>
</tr>
<tr>
<td>Skin rash and/or blistering</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
### IMPORTANT: PLEASE READ

#### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist immediately</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only if severe</td>
<td>In all cases</td>
</tr>
<tr>
<td>Hives and/or itching</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Difficulty to urinate</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Low blood pressure (hypotension): dizziness when rising to a standing position, impaired concentration and lightheadedness</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Yellow coloration of the skin (jaundice)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Dehydration and/or abnormal blood tests: dryness of the mouth, thirst, weakness, dizziness, fainting or loss of consciousness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, racing or irregular heartbeats, nausea and vomiting, sweating, increases in blood sugar levels, increased urination, mental confusion, headache</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Muscle problems: unexplained muscle pain, tenderness, weakness, cramps</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Pseudo–Bartter syndrome: abnormal blood tests, fatigue, muscle weakness, diarrhea, dehydration, increased thirst, increased urination, low blood pressure, irregular heartbeats</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Blurred vision</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist immediately</th>
<th>Stop taking drug and seek immediate emergency medical attention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only if severe</td>
<td>In all cases</td>
</tr>
<tr>
<td>Allergic reactions: eyes sensitive to light, tingling of fingers or toes, fever</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Blood clots: pain, swelling tenderness in your leg or arm, warm, red skin and a heavy feeling in the affected area</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Failure of the kidneys: weakness, trouble breathing, swelling, fast or irregular heartbeat, confusion, decrease or inability to urinate, loss of appetite, coma and death</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>In premature babies: discoloured urine and/or blood in the urine/diaper, fever and chills, vomiting, excessive crying or other signs the baby is in pain</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>In premature babies: poor weight gain</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Although not all of the above side effects are common, if you experience one of these while you are in the hospital or at home, talk to your doctor or pharmacist immediately.

This is not a complete list of side effects. For any unexpected effects while taking LASIX, contact your doctor or pharmacist.

### HOW TO STORE IT

Store your solution at room temperature (15° – 30°C). Protect from light.
There is an expiration date on the label. Do not use the medicine after this date.

Return any leftover solution to the pharmacist, unless the doctor tells you to keep them at home. As with all medicines, keep LASIX out of reach of children.

### REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

### MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.sanofi.ca or by contacting the sponsor, sanofi-aventis Canada Inc. at: 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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