PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]LASIX® ORAL SOLUTION

Furosemide oral solution

Solution, 10 mg / mL, Oral

Manufacturer standard

Diuretic

sanofi-aventis Canada Inc.
2905 Place Louis-R.-Renaud
Laval, Quebec H7V 0A3

Date of Initial Authorization:
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RECENT MAJOR CHANGES

Not Applicable

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LASIX ORAL SOLUTION® (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.
- The control of mild to moderate hypertension, used alone, 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 ORAL SOLUTION alone.

1.1 Pediatrics

When administered to children, LASIX ORAL SOLUTION therapy should be instituted in the hospital, in carefully selected patients, under close observation with frequent monitoring of serum electrolytes (*see 4 DOSAGE AND ADMINISTRATION*).

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

1.2 Geriatrics

Geriatrics (> 65 years of age)

Use in the geriatric population is associated with differences in safety. 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. (*see 7 WARNINGS AND PRECAUTIONS*).

2 CONTRAINDICATIONS

LASIX ORAL SOLUTION (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 4 DOSAGE AND ADMINISTRATION* 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 pre-coma or in states of electrolyte depletion until the basic condition is improved or corrected. Therapy with LASIX ORAL SOLUTION should not be initiated in these patients (*see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic*).
- Patients with severe dehydration, hypotension, hyponatremia, hypokalemia, or hypovolemia (*see 7 WARNINGS AND PRECAUTIONS* and 8 *ADVERSE REACTIONS*).
- Jaundiced newborn infants or infants suffering from diseases (e.g. Rh incompatibility, familial non-hemolytic jaundice, etc.) as furosemide may be capable of displacing bilirubin from albumin at least "*in vitro*". It can lead to hyperbilirubinemia and possibly kernicterus.
- Women that are breast-feeding (*see 7 WARNINGS AND PRECAUTIONS*).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

LASIX ORAL SOLUTION is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dosage schedule have to be adjusted to the individual patient's needs (see 4 Dosage and Administration).

The use of LASIX ORAL SOLUTION has been associated with exacerbation or activation of systemic lupus erythematosus.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Careful observations for changes in blood pressure must be made when LASIX ORAL SOLUTION 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 ORAL SOLUTION is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of LASIX ORAL SOLUTION, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

4.2 Recommended Dose and Dosage Adjustment

Adults

Edema

The usual initial dose of LASIX ORAL SOLUTION is 4 mL to 8 mL of 10 mg/mL. 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 2 mL to 4 mL of 10 mg/mL if necessary.

Maximum daily dose: 20 mL of 10 mg/mL. 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 ORAL SOLUTION is given for 2 to 4 consecutive days each week. With doses exceeding 12 mL/day of 10 mg/mL, careful clinical and laboratory observations are particularly advisable.

Hypertension

A dosage schedule of 2 mL to 4 mL of 10 mg/mL twice daily is recommended. Individualized therapy is of great importance. It is further recommended, if 4 mL twice daily of 10 mg/mL does not lead to a clinically satisfactory response, other antihypertensive agents should be added, rather than increase the dose of LASIX ORAL SOLUTION.

Pediatrics

LASIX ORAL SOLUTION 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 premature 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 ORAL SOLUTION is used in infants and children.

4.5 Missed dose

In case of a missed dose, patients may not notice any symptoms of the condition for which they are being treated for. However, please advise your patients to take the missed dose as soon as possible. And if it is almost time for their next dose, skip the missed dose and take the dose which is due as per the regular dosing schedule. Do not double dose.

5 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. hypovolemia, 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 designed to reduce absorption (e.g. activated charcoal).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

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

LASIX ORAL SOLUTION

Clear, slightly yellowish liquid, with an orange odour, containing 10 mg/mL furosemide. Available in bottles of 120 mL.

7 WARNINGS AND PRECAUTIONS

General

All patients receiving LASIX ORAL SOLUTION 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, oliguria, 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 ORAL SOLUTION 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 ORAL SOLUTION 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*).

The possibility exists of exacerbation or activation of systemic lupus erythematosus. Therapy with LASIX ORAL SOLUTION should be administered cautiously in patients with a history of lupus.

Concomitant use with risperidone

There is an increased risk of mortality in patients with dementia (*see 9 DRUG INTERACTIONS* Patients with dementia should be carefully monitored, especially their hydration status, as dehydration is an overall risk factor for mortality (*see 2 CONTRAINDICATIONS*).

Driving and Operating Machinery

LASIX ORAL SOLUTION 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 8 ADVERSE REACTIONS*).

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 2 CONTRAINDICATIONS*). Particularly careful monitoring is necessary in patients with Hepatorenal syndrome.

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 ORAL SOLUTION. 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:

- Premature infants. Renal function must be monitored and renal ultrasonography performed
- Patients with:
    - Hypoproteinemia. Cautious dose titration is require
    - Hypotension
    - A 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). Hepatorenal syndrome
    - latent and manifest Diabetes mellitus
    - Gout

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 ORAL SOLUTION and it is advisable to discontinue LASIX ORAL SOLUTION for one week prior to any elective surgery.

7.1 Special Populations

7.1.1. 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 fetus.
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 fetal 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 fetuses derived from treated dams as compared to the incidence of fetuses from the control group.

Treatment during pregnancy requires monitoring of fetal growth.

7.1.2 Breast-feeding

It should be noted that diuretics may partially inhibit lactation and that LASIX ORAL SOLUTION passes into the breast milk. Women must not breast-feed if they are treated with furosemide (*see 2 CONTRAINDICATIONS*).

7.1.3 Pediatrics

LASIX ORAL SOLUTION 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 ORAL SOLUTION may precipitate nephrocalcinosis/nephrolithiasis. When administered to premature infants with respiratory distress syndrome in the first few weeks of life, diuretic treatment with LASIX ORAL SOLUTION may accentuate the risk of a

patent ductus arteriosus (*see 7 WARNINGS AND PRECAUTIONS- Monitoring and Laboratory Tests*).

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

7.1.4 Geriatrics

Geriatrics (> 65 years of age**)**

Excessive diuresis induced by LASIX ORAL SOLUTION 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 ORAL SOLUTION 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.

8 ADVERSE REACTIONS

8.1 Adverse reaction overview

Serious adverse reactions with unknown frequency are thrombosis, nephrocalcinosis/nephrolithiasis in premature infants, renal failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and Drug Rash with Eosinophilia and Systemic Symptoms. The most commonly reported adverse reactions (≥ 10%) are electrolyte disturbances (including symptomatic), dehydration, hypovolaemia, (especially in elderly patients), increased blood creatinine and triglyceride levels, and hypotension, including orthostatic hypotension (*see 7 WARNINGS AND PRECAUTIONS, General*)."

8.2 Clinical Trial Adverse Reactions

This information is not available for this drug product.

8.5 Post-Market Adverse 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 ORAL SOLUTION, 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 7 WARNINGS AND PRECAUTIONS).*

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 ORAL SOLUTION 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 ORAL SOLUTION 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 pustolosis), lichenoid reactions 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 ORAL SOLUTION may accentuate the risk of a patent ductus arteriosus.

9 DRUG INTERACTIONS

9.2 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 7 WARNINGS AND PRECAUTIONS – Peri-Operative Considerations*).

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 ORAL SOLUTION to diabetic patients may result in possible decrease of diabetic control. Dosage adjustment 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 7 WARNINGS AND PRECAUTIONS).*

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

Non-steroidal anti-inflammatory drugs (NSAIDS, e.g. indomethacin, Acetylsalicylic acid, diclofenac, ibuprofen and naproxen.) may attenuate the effect of LASIX ORAL SOLUTION and may cause renal failure in case of pre-existing hypovolemia.

9.4 Drug-Drug Interactions

Table 2 - Established or Potential Drug-Drug Interactions

Proper Name	Source of Evidence	Effect	Clinical Comments
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	T	↓ furosemide diuretic effect	Anticonvulsant drugs (phenytoin, carbamazepine, phenobarbital), which, like furosemide, undergo significant renal tubular secretion, may also attenuate the effect of furosemide.
Antidiabetics			
Insulin, Metformin, Glipizide	T	↓ antidiabetic drug effect	The effects of antidiabetic drugs may be reduced.

Proper Name	Source of Evidence	Effect	Clinical Comments
Antihypertensive Agents			
ACE inhibitors Enalapril, Ramipril, Lisinopril	CT	↓ blood pressure and renal function	Especially in combination with ACE inhibitors, a marked hypotension may be seen sometimes progressing to shock. The concomitant administration of LASIX ORAL SOLUTION 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.
Angiotensin II receptor antagonists Irbesartan, valsartan, losartan	CT	↓ blood pressure and renal function	Especially in combination with angiotensin II receptor antagonists, a marked hypotension may be seen sometimes progressing to shock. The concomitant administration of LASIX ORAL SOLUTION 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.
Cephalosporins			
Cefazolin, cefadroxil	T	↓ renal function	Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Proper Name	Source of Evidence	Effect	Clinical Comments
Chloral Hydrate	C	—	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.
Chlorothiazides			
Hydro-chlorothiazide	T	—	The concurrent use of LASIX ORAL SOLUTION with hydrochlorothiazide has been reported to decrease hypercalciuria and to dissolve some calculi.
Cisplatin	T	↑ nephrotoxicity ↑ ototoxicity	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.
Cyclosporine	CT	—	Concomitant use of cyclosporine A and furosemide is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperurecemia and cyclosporine impairment of renal urate excretion.
Digitalis Glycosides	T	↓ potassium plasma concentration	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 ORAL SOLUTION therapy may be

Proper Name	Source of Evidence	Effect	Clinical Comments
			required (see 7 WARNINGS AND PRECAUTIONS).
Direct Renin Inhibitor			
Aliskiren	C / CT / T	↓ Plasma concentration of furosemide given orally	Aliskiren reduces plasma concentration of furosemide given orally. In patients treated with both aliskiren and oral furosemide, it is recommended to monitor for reduced diuretic effect and adjust the dose accordingly
Levothyroxine	C	↑ then ↓ thyroid hormones	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.
Lithium	T	↑ lithium plasma concentration	Renal clearance of lithium is decreased in patients receiving LASIX ORAL SOLUTION, 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.
Methotrexate	T	↓ furosemide diuretic effect	Methotrexate, which like furosemide, undergoes significant renal tubular secretion, may also attenuate the effect of furosemide.
Nephrotoxic Drugs			
Nephrotoxic Drugs Cisplatin, cyclosporin, Indomethacin	T	↑ nephrotoxicity	The harmful effects of nephrotoxic drugs on the kidney may be increased.

Proper Name	Source of Evidence	Effect	Clinical Comments
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)			
Indomethacin	CT	↓ furosemide diuretic effect	Clinical studies have shown that the administration of indomethacin can reduce the natriuretic and anti-hypertensive effect of LASIX ORAL SOLUTION in some patients. This response has been attributed to inhibition of prostaglandin synthesis by indomethacin. Therefore, when indomethacin is added to the treatment of a patient receiving LASIX ORAL SOLUTION, or LASIX ORAL SOLUTION is added to the treatment of a patient receiving indomethacin, the patient should be closely observed to determine if the desired effect of LASIX ORAL SOLUTION is obtained. Indomethacin blocks the LASIX ORAL SOLUTION-induced increase in plasma-renin activity. This fact should be kept in mind when evaluating plasma-renin activity in hypertensive patients.

Proper Name	Source of Evidence	Effect	Clinical Comments
Potassium-depleting Steroids			
Prednisone	T	↓ potassium plasma concentration	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 ORAL SOLUTION therapy may be required (see 7 WARNINGS AND PRECAUTIONS).
Probenecid	T	↓ furosemide diuretic effect	Probenecid, which like furosemide, undergoes significant renal tubular secretion, may also attenuate the effect of furosemide.
Radiocontrast Agents	CT	↑ radiocontrast nephropathy	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.

Proper Name	Source of Evidence	Effect	Clinical Comments
Risperidone	CT	—	A higher incidence of mortality was observed in elderly patients with dementia treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to elderly patients with dementia 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). 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 7 WARNING AND PRECAUTIONS
Salicylates			
Acetylsalicylic acid	T	↑ salicylate toxicity	Patients receiving high doses of salicylates in conjunction with LASIX ORAL SOLUTION may experience salicylate toxicity at lower doses because of competition for renal excretory sites.
Sucralfate	T	↓ furosemide absorption	Concurrent administration of LASIX ORAL SOLUTION and sucralfate should be avoided, as sucralfate reduces the absorption of furosemide from the intestine and hence weakens its effect.
Theophylline	T	↑ theophylline effect	The effects of theophylline may be increased.

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Animal experiments using stop-flow and micropuncture techniques have demonstrated that LASIX ORAL SOLUTION inhibits sodium reabsorption in the ascending limb of Henle's loop as well as in both proximal and distal tubules. The action of LASIX ORAL SOLUTION on the distal tubule is independent of any inhibitory effect on carbonic anhydrase or aldosterone.

LASIX ORAL SOLUTION may promote diuresis in cases which have previously proved resistant to other diuretics.

10.2 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.

10.3 Pharmacokinetics

Absorption

In humans, LASIX ORAL SOLUTION 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.

Distribution

In plasma, Furosemide is extensively bound to proteins mainly to albumin. The unbound fraction in plasma averages 2 - 4% at therapeutic concentrations. The apparent volume of distribution ranges between 0.1 to 0.2 L/kg in adults.

Metabolism:

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

Elimination

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 3 - Summary of furosemide's elimination kinetics

Subjects	Route of Administration	Dose (mg)	Rate of Administration	Biliary Excretion	Max. Serum Concentration	$t_{½}$ (hr)
Normal	Oral	40	—	10-15%	< 1μg /mL	4.0
Normal	I.V.	40	Bolus	10-15%	2.5 μg/mL	4.5
Renal insufficiency	I.V.	1000	25 mg/min.	60%	53 μg /mL	13.5
Renal insufficiency	I.V.	1000	4 mg/min.	—	29 μg /mL	—

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.

- **Pregnancy and Breast Feeding**

  Furosemide crosses the placental barrier and transfers to the fetus slowly. It is found in the fetus or newborn in the same concentrations as in the mother (*see 7 WARNINGS AND PRECAUTIONS, Pregnant Women).*
  Furosemide passes into the breast milk and may inhibit lactation (*see 7 WARNINGS AND PRECAUTIONS, Breast-feeding).*

- **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.

11 STORAGE, STABILITY AND DISPOSAL

Temperature

Oral solution: Store between 15° and 30°C.

Protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions applicable to this drug.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

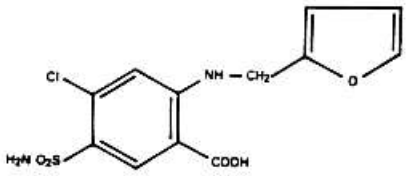
Drug Substance

Proper name: furosemide

Chemical name: 4-chloro-N-furfuryl-5-sulfamoyl-anthranilic acid

Molecular formula and molecular mass: $C_{12}H_{11}ClN_2O_5S$ (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).

14 CLINICAL TRIALS

The clinical data on which the original data was initially authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

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

Table 4 - ACUTE TOXICITY (LD_{50}) OF FUROSEMIDE (Approximate doses in mg/kg)

SPECIES	ORAL	INTRAVENOUS
Mice	1000	300
Adult Rats	4600	700
Newborn Rats	400	-
Rabbits	700	400
Dogs	2000	over 400

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.

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.

Reproductive and Developmental Toxicology:

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 fetal 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 fetuses derived from treated dams as compared to the incidence of fetuses from the control group.

DETAILED PHARMACOLOGY

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 the loop of Henle . 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.

17 SUPPORTING PRODUCT MONOGRAPHS

LASIX ORAL SOLUTION® (Oral Solution 10 mg/mL), Submission Control No: 211339, Product Monograph, sanofi-aventis Canada Inc. (February 21, 2018)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrLASIX® ORAL SOLUTION

Furosemide oral solution

Read this carefully before you start taking **LASIX ORAL SOLUTION** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LASIX ORAL SOLUTION**.

Serious Warnings and Precautions

- LASIX ORAL SOLUTION is a strong diuretic. Taking too much LASIX ORAL SOLUTION can cause you to lose too much water and too many electrolytes. You must be supervised by a healthcare professional while taking this medicine. Your healthcare professional will adjust your dose and your dosing schedule to treat your particular condition.
- LASIX ORAL SOLUTION may worsen or activate lupus (an autoimmune disease) in patients who have lupus or have had an episode of lupus. See the **Serious side effects and what to do about them** table for more information about this serious side effect.

What is LASIX ORAL SOLUTION used for?

LASIX ORAL SOLUTION is used in adults and children:

- to treat swelling in the body caused by excess fluid in the tissues (edema) due to a medical condition. This may include congestive heart failure, liver disease (cirrhosis), kidney disease, including nephrotic syndrome, or other medical conditions.
- alone to treat mild to moderate high blood pressure.
- in combination with other medicines to treat severe high blood pressure.

How does LASIX ORAL SOLUTION work?

LASIX ORAL SOLUTION belongs to a group of medicines called diuretics. It works by removing excess water from the body by making the kidneys produce more urine. This helps reduce swelling in the body and lower blood pressure.

What are the ingredients in LASIX ORAL SOLUTION?

Medicinal ingredients: Furosemide

Non-medicinal ingredients: Alcohol, butylated hydroxyanisol, butylated hydroxytoluene, glycerine, methylparaben, natural orange flavour, polysorbate 80, potassium sorbate, purified water, sodium hydroxide and sorbitol

LASIX ORAL SOLUTION comes in the following dosage forms:

Oral solution: 10 mg/mL

Do not use LASIX ORAL SOLUTION if:

- you are allergic to furosemide or any of the other ingredients in LASIX ORAL SOLUTION.
- you are allergic to sulfonamides, also known as "sulfa drugs". Ask your healthcare professional if you are unsure.
- your kidneys have completely stopped working.
- you have severe liver disease or have a decline in brain function, including coma, as a result of liver failure.
- you have been told you have low levels of electrolytes (salts such as sodium, potassium, calcium, magnesium, or chloride) in the blood.
- you are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- you have low blood volume.
- you have low blood pressure.
- your newborn infant has jaundice (yellowing of the skin or whites of eyes), or your infant suffers from a disease that has the potential of causing a build-up of bilirubin in the blood, which can even lead to a type of brain damage called kernicterus. This includes diseases such as Rh incompatibility, familial non-hemolytic jaundice, etc. Your child's healthcare professional will carefully assess their condition and decide if they should take LASIX ORAL SOLUTION.
- you are breastfeeding or planning to breastfeed.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child take LASIX ORAL SOLUTION. Talk about any health conditions or problems you or your child may have, including if you or your child:

- are taking any of the following medicines:
  - digitalis glycosides, used to treat various heart conditions.
  - risperidone, used to treat mental or mood disorders (e.g., schizophrenia, bipolar disorder). The combination of furosemide, the active ingredient in LASIX ORAL SOLUTION, and risperidone has been linked to a higher rate of death in elderly patient with dementia (loss of memory and other mental abilities).
  - medicines used to reduce inflammation such as certain steroids, or glucocorticoids.
  - medicines that are known to cause ear damage.

  Ask your healthcare professional if you are unsure.
- have difficulty urinating.
- have lupus, or have had an episode of lupus (an autoimmune disease).
- had or will have a kidney transplant.

- have been told you have low levels of protein in the blood.
- have high blood sugar or diabetes. LASIX ORAL SOLUTION may affect your blood sugar levels and accelerate the development of diabetes.
- intend to change your eating habits.
- have liver problems, including cirrhosis of the liver (permanent damage or scarring of the liver).
- have ascites (collection of fluid in spaces within your abdomen due to a medical condition).
- have kidney problems, including hepatorenal syndrome (kidneys stop working well in people with serious liver problems).
- have high levels of uric acid in the blood, or have gout. LASIX ORAL SOLUTION may make a gout attack more likely.
- was born prematurely (children).
- are planning to have surgery (including dental procedures).
- are at risk from a rapid fall in blood pressure (e.g., you have abnormal narrowing in the arteries that supply blood to your heart or brain).
- are pregnant, planning to become pregnant or think you might be pregnant.

Other warnings you should know about:

Diet: You should not be on a low-salt diet while taking LASIX ORAL SOLUTION. If you are taking LASIX ORAL SOLUTION for an extended period of time, your healthcare professional may recommend that you eat a diet rich in potassium. They may also recommend that you take potassium supplements, especially if you have been prescribed high doses of LASIX ORAL SOLUTION.

Hearing problems: LASIX ORAL SOLUTION may cause ringing in the ears, or temporary or permanent hearing loss, especially in children. In some cases, the onset of deafness was subtle at first but gradually worsened up to 6 months after treatment.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have surgery (including dental procedures). Your healthcare professional may ask you to stop taking LASIX ORAL SOLUTION a week before surgery. Follow their instructions carefully.

Pregnancy: It is not known if LASIX ORAL SOLUTION can harm an unborn baby. LASIX ORAL SOLUTION is not recommended during pregnancy or in women capable of becoming pregnant, unless your healthcare professional decides the benefits outweigh the potential risks to your baby. If it is decided that you should take LASIX ORAL SOLUTION during pregnancy, your healthcare professional will closely monitor your health and that of your baby. If you discover that you are pregnant while taking LASIX ORAL SOLUTION, tell your healthcare professional **right away.**

Breast-feeding: LASIX ORAL SOLUTION passes into breast milk and may harm your baby. Do not breast-feed while you are taking LASIX ORAL SOLUTION. Talk to your healthcare professional about other ways to feed your baby during this time. Diuretics, such as LASIX ORAL SOLUTION, may also reduce the amount of breast milk you produce.

Driving and using machines: LASIX ORAL SOLUTION can cause low blood pressure or other side effects that may affect your abilities, especially at the start of your treatment. Before doing tasks that require special attention, wait until you know how you respond to LASIX ORAL SOLUTION.

Infants and premature babies: If LASIX ORAL SOLUTION is given to infants or premature babies, they may be at higher risk for certain serious side effects. These include:

- **low blood calcium levels in infants**, which can lead to tetany. Tetany involves involuntary contraction of muscles, which leads to painful muscle spasms and stiff immovable muscles.
- **kidney stones in premature babies.**
- **a heart defect in premature babies whose lungs are not fully developed** when LASIX ORAL SOLUTION is given to them in their first few weeks of life.

See the **Serious side effects and what to do about them** table for more information on these and other serious side effects.

Adults (over 61 years of age): Side effects like dehydration, low blood volume, blood circulation failure, and potentially blood clots are more likely. Your healthcare professional may adjust your dose of LASIX ORAL SOLUTION and monitor your health closely during treatment.

Check-ups and testing: Your healthcare professional will do check-ups and tests while you are taking LASIX ORAL SOLUTION. These tests may include:

- blood tests to monitor:
  - the level of electrolytes (sodium, potassium, calcium, magnesium, or chloride) in the blood.
  - the level of carbon dioxide (CO_2) in the blood.
  - the level of sugar (glucose) in the blood.
  - the health of your blood, liver and kidneys.
- urine tests to monitor the level of sugar (glucose) in your urine.
- blood pressure checks to monitor your blood pressure.

Your healthcare professional will also:

- regularly monitor you for signs of electrolyte imbalances.
- monitor if you have problems urinating, especially when starting treatment with LASIX ORAL SOLUTION.

Tell your healthcare professional about all the medicines you or you child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LASIX ORAL SOLUTION:

- other diuretics (also known as "water pills"), which are used to help rid your body of salt and water, such as hydrochlorothiazide, or ethacrynic acid.
- medicines used to treat high blood pressure such as enalapril, ramipril, lisonipril, irbesartan, valsartan, losartan, and aliskiren.
- medicines that raise your blood pressure such as epinephrine (used to treat life-threatening allergic reactions).
- medicines used to reduce inflammation such as certain steroids, or glucocorticoids.
- medicines used to relieve pain, fever and inflammation such as non-steroidal anti-inflammatory drugs (NSAIDs), including indomethacin, acetylsalicylic acid (ASA), or other salicylates.
- muscle relaxants used during surgery or other procedures such as tubocurarine, or curare.
- medicines used to treat seizures such as carbamazepine, phenobarbital, or phenytoin.
- medicines used to treat bacterial infections such as cefazolin, cefadroxil, or aminoglycosides.
- sedatives, which are used to treat insomnia, reduce anxiety, or help put you to sleep before surgery or other procedures such as chloral hydrate, or phenobarbital.
- digitalis glycosides, used to treat various heart conditions.
- methotrexate, used to treat cancer and certain autoimmune disorders.
- cisplatin, used to treat cancer.
- cyclosporine, used to suppress the immune system.
- levothyroxine, used to treat an underactive thyroid gland.
- probenecid, used to treat gout.
- risperidone, used to treat mental or mood disorders (e.g., schizophrenia, bipolar disorder).
- lithium, used to treat manic episodes of bipolar disorder.
- carbenoxolone, used to treat lip sores and mouth ulcers.
- sucralfate, used to treat and prevent ulcers in the intestines.
- theophylline, used to treat asthma and other breathing problems.
- radiocontrast agents, used during radiological examinations.
- medicines used to treat diabetes, including insulin, metformin, and glipizide.
- medicines that are known to cause ear or kidney damage.
- laxatives.
- licorice.

Ask your healthcare professional if you are not sure if a medicine you or your child are taking is listed above.

How to take LASIX ORAL SOLUTION:

- Your or your child's healthcare professional will decide on the dose that is right for you or your child, and when it should be taken depending on your or your child's condition. Take LASIX ORAL SOLUTION exactly as they tell you.
- Never increase or decrease your or your child's dose unless your healthcare professional tells you to.
- LASIX ORAL SOLUTION should be taken on an empty stomach.
- In children, treatment with LASIX ORAL SOLUTION will be initiated in a hospital setting, under close observation with frequent blood tests to monitor electrolyte levels.
- This medicine was specifically prescribed for you or a child in your care. Do not give it to others, even if they have the same symptoms. Do not use it for conditions other than the one for which it was prescribed.

Usual dose:

Adults:

- To treat swelling: The usual dose is 4mL to 8mL of 10 mg/mL mg, taken 1 to 3 times a day. Your healthcare professional may adjust your dose depending on how you respond to LASIX ORAL SOLUTION. The maximum daily dose is 20 mL of 10 mg/mL.
- To treat high blood pressure: The usual dose is 2 mL to 4 mL of 10 mg/mL, twice daily.

Children:

- Your child's healthcare professional will determine the right dose based on your child's weight. Follow their instructions carefully.
- The usual starting dose for children is 0.5 to 1 mg for each kg they weigh in divided doses, 6 to 12 hours apart. The maximum daily dose is 2 mg for each kg they weigh. In newborn and premature babies, the maximum daily dose is 1 mg for each kg they weigh.

Overdose:

Signs of an overdose with LASIX ORAL SOLUTION may include:

- dehydration
- low electrolyte levels in the blood, which may cause you to feel weak, dizzy, confused, tired, have cramps or vomit.
- extremely low blood pressure that can lead to shock (rapid breathing, pale skin, cold and sweaty skin)
- a decline in brain function, including coma, in patients with liver problems (cirrhosis)
- severe kidney problems
- formation of one or more clots inside your blood vessels
- sudden change in mental status (delirium)
- sudden muscle weakness or paralysis (flaccid paralysis)

- lack of interest or emotions
- confusion

If you think you, or a person you are caring for, have taken too much LASIX ORAL SOLUTION, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using LASIX ORAL SOLUTION?

These are not all the possible side effects you may have when taking LASIX ORAL SOLUTION. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- blurred or yellow vision
- indigestion, diarrhea, constipation
- sweet taste
- nausea or vomiting
- skin rash, hives, itchy skin, purple-coloured spots on the skin
- feeling like you are spinning (vertigo)
- feeling pressure in the head
- dizziness or feeling lightheaded
- headache
- fainting
- burning or prickling sensation in the hands, arms, legs, or feet

LASIX ORAL SOLUTION can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Dehydration: dry mouth, increased thirst, feeling tired or sleepy, lack of energy, passing less urine, headache, dizziness,			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
low blood pressure, racing or irregular heart rate, fainting, confusion			
Electrolyte imbalance: dry mouth, feeling thirsty, feeling weak, lack of energy, drowsiness, restlessness, muscle pain or cramps, muscle fatigue, low blood pressure, irregular heartbeat, urinating less frequently, nausea, vomiting, high blood sugar			✓
COMMON			
Hypotension (low blood pressure): dizziness when rising to a standing position, impaired concentration and lightheadedness		✓	
Liver disorder: yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite, impaired brain function (trouble concentrating, confusion, reduced alertness, impaired judgement), mood changes, muscle jerks, trouble sleeping, breath smells sweet and musty, disorientation		✓	
Increased levels of uric acid in the blood: swelling, redness in the joints, sudden and intense attacks of joint pain (gout attack)		✓	
UNCOMMON			
Allergic reactions: sensitivity to light, tingling of fingers or toes, fever			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Hearing problems: ringing in the ears, deafness, sometimes non-reversible		✓	
Serious skin reactions: raised red or purple skin patches, possibly with blister or crust in the center, possibly swollen lips, mild itching or burning; blisters of different sizes; skin redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, can be accompanied with fever, chills, headache, cough, body aches or swollen glands, yellow skin or eyes, shortness of breath, chest pain or discomfort, feeling thirsty, urinate less frequently			✓
VERY RARE			
Acute pancreatitis (inflammation of the pancreas): abdominal pain that radiates to your back, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			✓
UNKNOWN FREQUENCY			
Muscle problems: unexplained muscle pain, tenderness, weakness, cramps		✓	
Pseudo-Bartter syndrome (an acid-base and electrolyte imbalance): fatigue, muscle weakness, diarrhea, dehydration, increased thirst, increased urination, low blood pressure, irregular heartbeats			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Severe allergic reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat			✓
Thrombosis (clot in a blood vessel): pain, swelling tenderness in your leg or arm, warm, red skin and a heavy feeling in the affected area			✓
Kidney failure (severe kidney problems): weakness, trouble breathing, swelling, fast or irregular heartbeat, confusion, decrease or inability to urinate, loss of appetite, coma and death			✓
Heart defect in premature babies whose lungs are not fully developed: fast breathing or shortness of breath, rapid heart rate, heart murmur, trouble feeding leading to poor weight gain, sweating when eating or crying, tires easily when eating or playing		✓	
Low blood calcium levels in infants: floppy muscles, fast heart rate, rapid breathing, trouble feeding leading to poor weight gain, jitteriness, seizures, involuntary muscle contractions and stiff immovable muscles (tetany).		✓	
Kidney stones in premature babies: blood in the urine, fever and chills, nausea and vomiting, sharp pain in back or side, constant need to urinate, pain		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
while urinating, inability to urinate or can urinate only a small amount, cloudy or bad smelling urine			
Increased blood sugar: frequent urination, thirst and hunger		✓	
Rhabdomyolysis (breakdown of damaged muscle): muscle tenderness, weakness, red-brown (tea-coloured) urine			✓
Worsening or activation of lupus: fatigue, fever, joint pain, stiffness and swelling, rash on the face that covers the cheeks and the bridge of the nose or rashes elsewhere on the body, skin lesions, shortness of breath, chest pain, dry eyes, headaches, confusion and memory loss		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store your solution at room temperature (15°C – 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 your healthcare professional tells you to keep them at home.
- Keep out of reach and sight of children.

If you want more information about LASIX ORAL SOLUTION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

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