

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrLASIX® SPECIAL**

Furosemide tablets

Tablets, 500 mg, Oral

Manufacturer standard

Diuretic

sanofi-aventis Canada Inc.  
1755 Steeles Avenue West  
Toronto, ON  
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## RECENT MAJOR CHANGES

Not applicable

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## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **1 INDICATIONS**

LASIX® SPECIAL (furosemide) is indicated:

- as an adjuvant treatment of oliguria
- in the promotion of diuresis in the treatment of edema in selected patients with:
  - acute renal failure, e.g. in the postoperative phase and in association with septic infections;
  - chronic renal failure with fluid retention, both in the predialysis phase and when dialysis has become unavoidable, especially in the presence of acute pulmonary edema;
  - Nephrotic syndrome with severe impairment of renal function, e.g. in chronic glomerular nephritis, lupus erythematosus (*see 7 WARNINGS AND PRECAUTIONS, General*)
  - Kimmelstiel-Wilson syndrome.

LASIX® SPECIAL (furosemide 500 mg) IS A HIGH-DOSAGE FORMULATION OF FUROSEMIDE AND IS INTENDED EXCLUSIVELY FOR PATIENTS WITH SEVERELY IMPAIRED RENAL FUNCTION. LASIX SPECIAL IS TO BE USED UNDER STRICT MEDICAL SUPERVISION IN A HOSPITAL SETTING (*see 4 DOSAGE AND ADMINISTRATION*).

#### **1.1 Pediatrics**

##### Pediatrics (Newborn to 15 years)

LASIX SPECIAL is not recommended for the pediatric population (*see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics*).

#### **1.2 Geriatrics**

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

Use in the geriatric population is associated with differences in safety. Dose selection for the elderly patients should be cautious, 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 SPECIAL 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING* Patients allergic to

sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.

- Patients with complete renal shutdown and glomerular filtration rate below 5 mL/min.
- Patients whose glomerular filtration rate is above 20 mL/min. In such cases, it might cause extremely severe water and electrolyte losses
- Patients with hepatic cirrhosis, patients with renal failure due to poisoning with nephrotoxic or hepatotoxic substances and patients with renal failure accompanied by hepatic coma and precoma (*see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS*).
- Patients with severe dehydration, hypotension, hyponatremia, hypokalemia or hypovolemia (*see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS*).
- Children (Newborn -15 years)
- Women that are breastfeeding (*see 7 WARNINGS AND PRECAUTIONS*).

### **3 SERIOUS WARNINGS AND PRECAUTIONS**

#### **Serious Warnings and Precautions**

LASIX SPECIAL 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 Dosage and Administration).

The use of furosemide has been associated with exacerbation or activation of systemic lupus erythematosus.

### **4 DOSAGE AND ADMINISTRATION**

#### **4.1 Dosing Considerations**

LASIX SPECIAL is to be used under strict medical supervision in a hospital setting.

THE HIGH-DOSAGE FORMULATION LASIX SPECIAL IS INTENDED EXCLUSIVELY FOR SELECTED PATIENTS WITH SEVERELY IMPAIRED GLOMERULAR FILTRATION (GFR of less than 20 mL/min. but greater than 5 mL/min.), WHO HAVE NOT RESPONDED TO CONVENTIONAL DOSES OF FUROSEMIDE

When LASIX SPECIAL is used in high doses, careful attention much be paid to the following:

- If the patient is in shock, hypovolemia and hypotension must be corrected by appropriate measures before starting therapy.

- Any serious abnormalities of serum electrolytes or acid-base balance must be corrected before starting therapy
- When treating patients with conditions likely to interfere with micturition, such as prostatic hypertrophy or disturbed consciousness, it is absolutely essential to ensure free urinary drainage.
- Because of the wide and unpredictable individual variations in responsiveness, it is important to adjust dosage and route of administration to individual needs.
- Once the desired rise in urinary output has begun, exact balance of water intake and water output must be maintained throughout the course of treatment, so as to avoid hypovolemia or hypotension. Careful electrolyte replacement is also necessary.

The dosage of high strength LASIX SPECIAL given below is for adults only.

The administration of large doses of furosemide in children has been associated with permanent deafness (*See 7 WARNINGS AND PRECAUTIONS*).

#### **4.2 Recommended Dose and Dosage Adjustment**

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

For selected patients with advanced chronic renal failure, diuretic therapy may be started with lower oral doses of furosemide, e.g. 80-160 mg/day. If conventional doses fail to produce an adequate diuresis, a single dose of 250 mg may be given as a starting dose. If a satisfactory diuresis does not ensue within 4-6 hours, the initial dose may be doubled to 500 mg. The maximum daily dose of LASIX SPECIAL is 1000 mg and this should not be exceeded.

The criterion of optimal dosage is a urinary output of at least 2.5 litres per day.

### **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.

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

#### **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 (e.g. activated charcoal).

## 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	Tablet 500 mg	Corn starch, colloidal silicon dioxide, D&C Yellow #10, FD&C Yellow #6, lactose monohydrate, magnesium stearate, powdered cellulose, sodium starch glycolate and talc.

**Tablets, 500 mg:** Yellow, round, one side double-scored. On the scored side, are debossed the letters “D”, “L”, “X” between the score lines. Other side of the tablet is debossed with the Hoechst “Tower and Bridge” logo. Each tablet contains 500 mg furosemide in HDPE bottles of 20.

## 7 WARNINGS AND PRECAUTIONS

### General

All patients receiving LASIX SPECIAL 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 or potassium-depleting steroids. Potassium supplementation, diminution in dose, or discontinuation of LASIX SPECIAL 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 SPECIAL therapy.

During treatment with LASIX SPECIAL, extreme care must always be taken to adjust dosage to individual requirements.

Since furosemide is a sulfonamide derivative, it should be not be used in patients with known sulfonamide sensitivity (*see 2 CONTRAINDICATIONS*).

Urinary outflow must be secured. Patients with urinary outflow require careful monitoring, especially during the initial stages of treatment (*see 8 ADVERSE REACTIONS, Post-Market Adverse Drug Reactions-Renal and urinary disorders*).

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

### **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 SPECIAL 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. (The 500 mg furosemide tablet is for adults only). 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.

### **Monitoring and Laboratory Tests**

Frequent serum electrolyte, creatinine and CO<sub>2</sub> 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 SPECIAL. 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.
- 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 or curare-type muscle relaxants. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with LASIX SPECIAL and it is advisable to discontinue LASIX SPECIAL 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 SPECIAL passes into the breast milk. Women must not breast-feed if they are treated with furosemide (*see 2 CONTRAINDICATIONS*).

### **7.1.3 Pediatrics**

#### Pediatrics (newborn-15 years)

LASIX SPECIAL is not recommended for pediatric use (*see 2 CONTRAINDICATIONS*).

LASIX SPECIAL may lower serum calcium levels, and rare cases of tetany have been reported.

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.

### **7.1.4 Geriatrics**

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

Excessive diuresis induced by LASIX SPECIAL 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 SPECIAL 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 ( $\geq 10\%$ ) 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 occurrences of sweet taste have 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 SPECIAL, 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 SPECIAL 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 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 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 SPECIAL 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 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 SPECIAL is administered, since LASIX SPECIAL potentiates their hypotensive effect.

Non-steroidal anti-inflammatory drugs (e.g. indomethacin, acetyl-salicylic acid) may attenuate the effect of LASIX SPECIAL 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 comment
<b>Anticonvulsants</b>			
Carbamazepine Phenobarbital Phenytoin	T	↓ furosemide diuretic effect	may also attenuate the effect of furosemide.
Antidiabetics	T	↓ antidiabetic drug effect	The effects of antidiabetic drugs may be reduced.
<b>Antihypertensive Agents</b>			
ACE inhibitors	CT	↓ blood pressure and renal function	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.

Proper Name	Source of Evidence	Effect	Clinical comment
Angiotensin II receptor antagonists	CT	↓ blood pressure and renal function	The concomitant administration of LASIX SPECIAL 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	T	↓ renal function	Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.
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	T	—	The concurrent use of LASIX SPECIAL with chlorothiazide has been reported to decrease hypercalciuria and to dissolve some calculi.

Proper Name	Source of Evidence	Effect	Clinical comment
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 hyperuricemia 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 SPECIAL therapy may be required ( <i>see 7 WARNINGS AND PRECAUTIONS</i> ).

Proper Name	Source of Evidence	Effect	Clinical comment
<b>Direct Renin Inhibitor</b>			
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 SPECIAL, 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.
<b>Nephrotoxic Drugs</b>			

Proper Name	Source of Evidence	Effect	Clinical comment
Cisplatin, cyclosporin, Indomethacin	T	↑ nephrotoxicity	The harmful effects of nephrotoxic drugs on the kidney may be increased.
<b>Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)</b>			
Indomethacin	CT	↓ furosemide diuretic effect	<p>Clinical studies have shown that the administration of indomethacin can reduce the natriuretic and anti-hypertensive effect of LASIX SPECIAL 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 SPECIAL, or LASIX SPECIAL is added to the treatment of a patient receiving indomethacin, the patient should be closely observed to determine if the desired effect of LASIX SPECIAL is obtained.</p> <p>Indomethacin blocks the LASIX SPECIAL-induced increase in plasma-renin activity. This fact should be kept in mind when evaluating plasma-renin activity in hypertensive patients.</p>

Proper Name	Source of Evidence	Effect	Clinical comment
Potassium-depleting Steroids	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 SPECIAL therapy may be required ( <i>see 7 WARNINGS AND PRECAUTIONS</i> ).
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 comment
Risperidone	CT	----	<p>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).</p> <p>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.</p>
Salicylates	T	↑ salicylate toxicity	<p>Patients receiving high doses of salicylates in conjunction with LASIX SPECIAL may experience salicylate toxicity at lower doses because of competition for renal excretory sites.</p>
Sucralfate	T	↓ furosemide absorption	<p>Concurrent administration of LASIX SPECIAL and sucralfate should be avoided, as sucralfate reduces the absorption of furosemide from the intestine and hence weakens its effect.</p>

Proper Name	Source of Evidence	Effect	Clinical comment
Theophylline	T	↑ theophylline effect	The effects of theophylline may be increased; theophylline levels should be monitored during treatment

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

Interactions with other drugs have not been established.

### 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 furosemide inhibits sodium reabsorption in the ascending limb of Henle's loop as well as in both proximal and distal tubules. The action of LASIX SPECIAL on the distal tubule is independent of any inhibitory effect on carbonic anhydrase or aldosterone.

Furosemide 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.

In a randomized, open-label, two-period cross-over Phase I study in 12 chronic renal failure patients under peritoneal dialysis comparing a single dose of LASIX SPECIAL tablet 500 mg orally to furosemide injection 250 mg IV, there was no statistically significant difference in cumulative urinary output over 24 hours and in all time points (6, 12 and 24 hours) for both

formulations with respect to adjusted means of urinary volume and weight.

At 6 h after administration, adjusted means in urine chloride concentrations were statistically significantly higher in patients receiving furosemide 250 mg IV, while at 24 h adjusted means in urine sodium and calcium concentrations were statistically significantly higher in patients receiving LASIX SPECIAL 500 mg orally. Changes of adjusted means from baseline in these urinary electrolytes at other time points were not statistically significant between the two formulations.

Changes in adjusted means from baseline in other urinary electrolytes (potassium and magnesium), urea and creatinine concentrations, were not statistically significant between both formulations at any time point (6, 12 and 24 hours).

### 10.3 Pharmacokinetics

#### Absorption

In humans, LASIX SPECIAL 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 a Phase I study conducted in 12 chronic renal failure patients, a single oral dose of a 500 mg tablet of LASIX SPECIAL was shown to be 51.9% bioavailable when compared to a single dose of furosemide injection 250 mg IV (see 10 CLINICAL PHARMACOLOGY, Pharmacodynamics).

#### 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 <sub>½</sub> (hr)
Normal	Oral	40	—	10-15%	< 1mcg /mL	4.0
Renal insufficiency	Oral	500	-	-	15.1 mcg/mL	4.6

## Special Populations and Conditions

- **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 of 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 continuous ambulatory peritoneal dialysis.

## 11 STORAGE, STABILITY AND DISPOSAL

Tablets: Store between 15° and 25°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

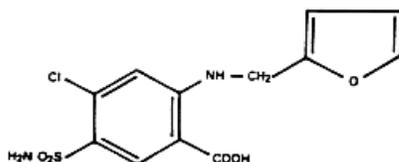
#### Drug Substance

Proper name: furosemide

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

Molecular formula and molecular mass: C<sub>12</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>5</sub>S and 330.7

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

Clinical trial data

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<sub>50</sub>) OF FUROSEMIDE (Approximate doses in mg/kg)**

SPECIES	ORAL	INTRAVENOUS
Mice	1000	300
Adult Rats	4600	700

SPECIES	ORAL	INTRAVENOUS
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 in 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.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

#### PrLASIX® SPECIAL

#### Furosemide tablets

Read this carefully before you start taking **LASIX SPECIAL** 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 SPECIAL**.

#### Serious Warnings and Precautions

- LASIX SPECIAL is a strong diuretic. Diuretics are also known as “water pills”. Taking too much LASIX SPECIAL 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 SPECIAL 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 SPECIAL used for?

- LASIX SPECIAL is used to help treat low urine output and excess fluid buildup in the body (edema) due to:
  - sudden kidney failure (a common complication of major surgery or sepsis);
  - chronic kidney failure with excess fluid buildup in the body, especially in the lungs (pulmonary edema). LASIX SPECIAL can be used before there is a need for dialysis or during dialysis;
  - a kidney disorder called nephrotic syndrome, which causes your body to pass too much protein in your urine, combined with a severe loss in kidney function (e.g., due to chronic glomerular nephritis, lupus erythematosus, or Kimmelstiel-Wilson syndrome).
- LASIX SPECIAL is a high-dosage formulation of furosemide. It is intended only in patients with severe kidney problems. A healthcare professional will supervise you while you take this medicine in the hospital.

#### How does LASIX SPECIAL work?

LASIX SPECIAL 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 excess fluid buildup in the body.

## **What are the ingredients in LASIX SPECIAL?**

Medicinal ingredients: Furosemide

Non-medicinal ingredients:

Colloidal silicon dioxide, corn starch, D&C Yellow #10, FD&C Yellow #6, lactose monohydrate, magnesium stearate, powdered cellulose, sodium starch glycolate and talc.

## **LASIX SPECIAL comes in the following dosage forms:**

Tablets: 500 mg

### **Do not use LASIX SPECIAL if:**

- you are allergic to furosemide or any of the other ingredients in LASIX SPECIAL.
- you are allergic to sulfonamides, also known as “sulfa drugs”. Ask your healthcare professional if you are unsure.
- you have kidney failure. This includes if:
  - you have it due to taking substances or medicines that are known to cause kidney or liver damage.
  - it is accompanied by a decline in brain function, including coma, as a result of liver failure.
- you have severe kidney damage. Taking LASIX SPECIAL may cause extreme water and electrolyte losses. Your healthcare professional will carefully assess your kidney function and decide if you should take LASIX SPECIAL.
- you have cirrhosis of the liver (permanent damage or scarring of the liver).
- you have been told you have low electrolyte levels (such as sodium or potassium) in the blood.
- you are dehydrated or suffer from excessive vomiting, diarrhea, or sweating.
- you have low blood volume.
- you have low blood pressure.
- you are below 15 years of age.
- you are breastfeeding or planning to breastfeed.

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

- 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 SPECIAL, 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). LASIX SPECIAL may activate or worsen your condition.
- had or will have a kidney transplant.
- have been told you have low levels of protein, chloride, magnesium, or calcium in the blood.
- have high blood sugar or diabetes. LASIX SPECIAL may affect your blood sugar levels and accelerate the development of diabetes.
- intend to change your eating habits.
- have liver problems.
- 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 SPECIAL may make a gout attack more likely.
- 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 SPECIAL. If you are taking LASIX SPECIAL 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 SPECIAL.

**Hearing problems:** LASIX SPECIAL may cause ringing in the ears, or temporary or permanent hearing loss.

**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 SPECIAL a week before your surgery. Follow their instructions carefully.

**Pregnancy:** It is not known if LASIX SPECIAL can harm an unborn baby. LASIX SPECIAL 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 can take LASIX SPECIAL 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 SPECIAL, tell your healthcare professional **right away**.

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

**Driving and using machines:** LASIX SPECIAL 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 SPECIAL.

**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 SPECIAL. They will monitor your health during your treatment.

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

- blood tests to monitor:
  - the level of electrolytes (sodium, potassium, calcium, magnesium, or chloride) in your blood.
  - the level of carbon dioxide (CO<sub>2</sub>) in your blood.
  - the level of sugar (glucose) in your 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 SPECIAL.

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

**The following may interact with LASIX SPECIAL:**

- 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, lisinopril, 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 are taking is listed above.

#### **How to take LASIX SPECIAL:**

- Treatment with LASIX SPECIAL will be initiated in a hospital setting, under close observation with frequent blood tests to monitor electrolyte levels.
- Swallow tablets whole with a glass of water.
- Never increase or decrease your dose unless your healthcare professional tells you to.
- This medicine was specifically prescribed for you. 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:**

- Your healthcare professional will decide on the dose that is right for you, and when it should be taken depending on your condition. Take LASIX SPECIAL exactly as they tell you.

- The maximum daily dose is 1000 mg.

**Overdose:**

Signs of an overdose with LASIX SPECIAL 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 SPECIAL, 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 SPECIAL?**

These are not all the possible side effects you may have when taking LASIX SPECIAL. 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 SPECIAL can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

<b>Serious side effects and what to do about them</b>			
<b>Symptom / effect</b>	<b>Talk to your healthcare professional</b>		<b>Stop taking drug and get immediate medical help</b>
	<b>Only if severe</b>	<b>In all cases</b>	
<b>VERY COMMON</b>			
<b>Dehydration:</b> dry mouth, increased thirst, feeling tired or sleepy, lack of energy, passing less urine, headache, dizziness, low blood pressure, racing or irregular heart rate, fainting, confusion			✓
<b>Electrolyte imbalance:</b> 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			✓
<b>COMMON</b>			
<b>Hypotension</b> (low blood pressure): dizziness when rising to a standing position, impaired concentration and lightheadedness		✓	
<b>Liver disorder:</b> 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,		✓	

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	
breath smells sweet and musty, disorientation			
<b>Increased levels of uric acid in the blood:</b> swelling, redness in the joints, sudden and intense attacks of joint pain (gout attack)		✓	
<b>UNCOMMON</b>			
<b>Allergic reactions:</b> sensitivity to light, tingling of fingers or toes, fever			✓
<b>Hearing problems:</b> ringing in the ears, deafness, both permanent and reversible		✓	
<b>Serious skin reactions:</b> 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			✓
<b>VERY RARE</b>			
<b>Acute pancreatitis</b> (inflammation of the pancreas): abdominal pain that radiates to your back, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen			✓
<b>UNKNOWN FREQUENCY</b>			

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	
<b>Muscle problems:</b> unexplained muscle pain, tenderness, weakness, cramps		✓	
<b>Pseudo-Bartter syndrome</b> (an acid-base and electrolyte imbalance): fatigue, muscle weakness, diarrhea, dehydration, increased thirst, increased urination, low blood pressure, irregular heartbeats			✓
<b>Severe allergic reactions:</b> sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat			✓
<b>Thrombosis</b> (clot in a blood vessel): pain, swelling, tenderness in your leg or arm; warm, red skin and a heavy feeling in the affected area			✓
<b>Kidney failure</b> (severe kidney problems): weakness, trouble breathing, swelling, fast or irregular heartbeat, confusion, decrease or inability to urinate, loss of appetite, coma and death			✓
<b>Increased blood sugar:</b> frequent urination, thirst and hunger		✓	
<b>Worsening or activation of lupus:</b> 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 tablets at room temperature (15°C – 25°C). Protect from light.
- There is an expiration date on the label. Do not use the medicine after this date.
- Return any leftover tablets 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 SPECIAL:**

- 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](http://www.sanofi.ca), or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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