

PRODUCT MONOGRAPH

^{Pr}LASIX[®] SPECIAL
furosemide tablets, Manufacturer standard
Tablets 500 mg

Diuretic

ATC Code: C03CA01

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^{Pr}LASIX[®] Special

(furosemide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal 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.

INDICATIONS AND CLINICAL USE

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 DOSAGE AND ADMINISTRATION).

High doses of LASIX SPECIAL may be used as an adjuvant treatment of oliguria and 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;
- in selected patients with 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;
- in selected patients with the nephrotic syndrome with severe impairment of renal function, e.g. in chronic glomerular nephritis, lupus erythematosus (see WARNINGS AND PRECAUTIONS section – General) and Kimmelstiel-Wilson syndrome.

Pediatrics (newborn-15 years)

LASIX SPECIAL is not recommended for pediatric use (see WARNINGS AND PRECAUTIONS section, under Special Populations, Pediatrics).

Geriatrics (> 61 years of age)

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

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 the Dosage Forms, Composition and Packaging section of the product monograph. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonyleureas) 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 WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).
- Severe hyponatremia, hypokalemia, hypovolemia, dehydration or hypotension must be regarded as contraindications until serum electrolytes and fluid balance and blood pressure have been restored to normal levels (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).
- As furosemide may be capable of displacing bilirubin from albumin at least "*in vitro*", it should not be administered to jaundiced newborn infants or to infants suffering from diseases (e.g. Rh incompatibility, familial non-hemolytic jaundice, etc.) with the potential of causing hyperbilirubinemia and possibly kernicterus.
- Women must not breast-feed if they are treated with furosemide (see WARNINGS AND PRECAUTIONS section).

WARNINGS AND PRECAUTIONS

General

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

All patients receiving LASIX 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 used with caution in patients with known sulfonamide sensitivity.

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

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

Concomitant use with risperidone

In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality (see CONTRAINDICATIONS section) and should therefore be avoided in elderly patients with dementia.

Carcinogenesis and Mutagenesis

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

In a carcinogenicity study, rats were administered furosemide in daily doses of 15 and 30 mg/kg body weight. Male rats in the 15 mg/kg-dose category, but not in the 30 mg/kg-dose category, showed a marginal increase in uncommon tumours.

Mutagenicity: In in-vitro tests on bacteria and mammalian cells, both positive and negative results have been obtained. Induction of gene and chromosome mutations, however, has been observed only where furosemide reached cytotoxic concentrations.

Ear/Nose/Throat

Cases of tinnitus and reversible deafness have been reported. There have also been some reports of cases, the majority in children undergoing renal transplantation, in which permanent deafness has occurred. In these latter cases, the onset of deafness was usually insidious and gradually progressive up to 6 months after furosemide therapy. (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.

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.

Special Populations

Pregnant Women

The teratogenic and embryotoxic potential of furosemide in humans is unknown. The drug should not be used in pregnant women or in women of childbearing potential unless in the opinion of the attending physician the benefits to the patient outweigh the possible risk to the 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 foetal lethality which can precede maternal deaths.

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

Treatment during pregnancy requires monitoring of fetal growth.

Nursing Women

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

Pediatrics (newborn-15 years)

LASIX SPECIAL is not recommended for pediatric use.

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.

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.

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 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.
- patients with hypotension
- patients who would be at particular risk from a pronounced fall in blood pressure (e.g. patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain).
- patients with hepatorenal syndrome.
- patients with latent and manifest diabetes mellitus
- patients with gout

Occupational Hazards

LASIX 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 ADVERSE REACTIONS section).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

No data available.

Post-Market Adverse Drug Reactions

Adverse reactions are categorized below by body system.

Blood and lymphatic system disorders

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

Ear and Labyrinth disorders

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

Vertigo has been reported.

Eye disorders

Xanthopsia and blurred vision have been reported.

Gastrointestinal disorders

Acute pancreatitis, oral and gastric burning, diarrhea, nausea, vomiting and constipation have been reported. Rare 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 angitis.

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 WARNINGS AND PRECAUTIONS section).

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

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

Treatment with LASIX 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.

DRUG INTERACTIONS

Overview

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

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

Glucocorticoids, carbenoxolone and licorice may also increase potassium loss.

Administration of LASIX 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 WARNINGS AND PRECAUTIONS section).

In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when LASIX 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.

Drug-Drug Interactions

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

Established or Predicted Drug-Drug Interactions

Proper Name	Ref	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			
Antidiabetics	T	↓ antidiabetic drug effect	The effects of antidiabetic drugs may be reduced.

Proper Name	Ref	Effect	Clinical Comments
Antihypertensive Agents			
ACE inhibitors	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 SPECIAL 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	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 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			
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			
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			
Chlorothiazides	T	—	The concurrent use of LASIX SPECIAL with chlorothiazide has been reported to decrease hypercalciuria and to dissolve some calculi.
Cisplatin			
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.

Proper Name	Ref	Effect	Clinical Comments
Cyclosporine			
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			
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 (see WARNINGS AND PRECAUTIONS).
Levothyroxine			
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			
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			
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	T	↑ nephrotoxicity	The harmful effects of nephrotoxic drugs on the kidney may be increased.
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 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. Indomethacin blocks the

Proper Name	Ref	Effect	Clinical Comments
			LASIX SPECIAL-induced increase in plasma-renin activity. This fact should be kept in mind when evaluating plasma-renin activity in hypertensive patients.
Potassium-depleting Steroids			
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 (see WARNINGS AND PRECAUTIONS).
Probenecid			
Probenecid	T	↓ furosemide diuretic effect	Probenecid, which like furosemide, undergoes significant renal tubular secretion, may also attenuate the effect of furosemide.
Radiocontrast Agents			
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.
Risperidone			
Risperidone	CT	—	Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use. See PRECAUTIONS section, regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.
Salicylates			
Salicylates	T	↑ salicylate toxicity	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.
Sucralfate			
Sucralfate	T	↓ furosemide absorption	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.
Theophylline			
Theophylline	T	↑ theophylline effect	The effects of theophylline may be increased.

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

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal product have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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 LASIX (SEE INDICATIONS AND CLINICAL USE).

WHEN LASIX SPECIAL IS USED IN HIGH DOSES CAREFUL ATTENTION MUST BE PAID TO THE FOLLOWING POINTS:

- 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 BEFOREHAND.
- 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 WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

Initial dose: The dose of furosemide which has been found to produce an effective diuresis when given intravenously is used as the initial dose.

For the initial intravenous dose, follow the manufacturer's dosage recommendations for the administration of intravenous furosemide as stated in the appropriate Product Monograph.

Additional dose: Should the initial dose fail to produce an adequate increase (at least 40-50 mL) in urinary output within 4-6 hours, the dose may be raised by 250 to 500 mg at a time.

For selected patients with advanced chronic renal failure, diuretic therapy may be started with LASIX orally. If conventional doses (80 to 160 mg orally) fail to produce an adequate diuresis, a single dose of 250 mg is 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 criterion of optimal dosage is a urinary output of at least 2.5 litres per day.

A maximum daily dose of 1000 mg should not be exceeded.

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 by measures such as gastric lavage or those designed to reduce absorption (e.g. activated charcoal).

ACTION AND CLINICAL PHARMACOLOGY

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.

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).

Pharmacokinetics

Absorption

In man, 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.

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 Pharmacodynamics section).

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

Excretion

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

The following table summarizes the elimination kinetics of furosemide.

Table 1 - Summary of furosemide's elimination kinetics

Subjects	Route of Administration	Dose (mg)	Rate of Administration	Biliary Excretion	Max. Serum Concentration	t_{1/2} (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	—
Renal insufficiency	Oral	500	-	-	15.1 µg/mL	4.6

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-conceptual age of more than 33 weeks.

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

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

Gender: Data unavailable.

Race: Data unavailable.

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

Renal Insufficiency: In renal failure, the elimination 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 haemodialysis, peritoneal dialysis and CAPD.

Genetic Polymorphism: Data unavailable.

STORAGE AND STABILITY

Temperature

Tablets: Store between 15° and 25°C.

Light

Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Oral

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.

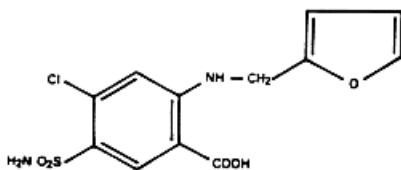
Non-medicinal ingredients: Corn starch, colloidal silicon dioxide, D&C Yellow #10, FD&C Yellow #6, lactose monohydrate, magnesium stearate, powdered cellulose, sodium starch glycolate and talc.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	furosemide
Chemical name:	4-chloro-N-furfuryl-5-sulfamoyl-anthranilic acid
Molecular formula:	$C_{12}H_{11}ClN_2O_5S$
Molecular mass:	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).

CLINICAL TRIALS

No data available.

DETAILED PHARMACOLOGY

LASIX SPECIAL has no significant pharmacological effects other than on the renal function.

Renal Pharmacology

In dogs, furosemide demonstrated diuretic properties. Diuresis and sodium excretion were induced by doses of 0.125 mg/kg administered intravenously or 0.5 mg administered orally. Maximum water and sodium excretion is obtained by oral and intravenous doses of 12.5 and 25 mg/kg respectively. Increased potassium excretion can only be demonstrated with doses exceeding 1 mg/kg. The onset of action is rapid after intravenous and oral administration and the duration of activity is approximately 2 and 4 hours respectively.

Furosemide produces an immediate diuresis after intravenous administration and is effective unilaterally after injection into a renal artery. Its action, therefore, is directly on the kidney. The diuretic response is prompt and relatively brief. At the peak of diuretic response 30-40% of filtered sodium load may be excreted, along with some potassium and with chloride as the major anion. Furosemide augments the potassium output as a result of increased distal potassium secretion. Its diuretic action is independent of changes in acid-base balance. Under conditions of acidosis or alkalosis the diuretic produces chloruresis without augmentation of bicarbonate excretion. It does not inhibit carbonic anhydrase.

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

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

TOXICOLOGY

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

Table 2 - ACUTE TOXICITY (LD₅₀) 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.

Reproductive and teratological studies

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

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

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IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

Pr LASIX[®] SPECIAL
(furosemide tablets, Manufacturer standard)

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

ABOUT THIS MEDICATION

What the medication is used for:
LASIX SPECIAL IS A HIGH-DOSE MEDICATION INTENDED EXCLUSIVELY FOR PATIENTS WITH SEVERELY IMPAIRED KIDNEY FUNCTION. LASIX SPECIAL IS TO BE USED UNDER STRICT MEDICAL SUPERVISION IN A HOSPITAL SETTING.

LASIX SPECIAL may be used as an aid in the treatment of conditions such as kidney disease, low urine production, edema (water retention), acute/chronic kidney failure before starting on dialysis and once on dialysis for patients with continued water in their lungs (pulmonary edema).

What it does:

LASIX SPECIAL belongs to a group of medicines known as diuretic drugs which improve the elimination of water and salts (electrolytes) in the urine.

When it should not be used:

Do not use LASIX SPECIAL

- If you are allergic to it or to any of the components of its formulation (for list of components see the section on "What the non-medicinal ingredients are").
- If you are allergic to any sulfonamide-derived drugs. Ask your physician or pharmacist if you are not sure what sulfonamide-derived drugs are.
- If you have hypokalemia (low potassium blood levels).
- If you have hyponatremia (low sodium blood levels).
- If you have low blood pressure.
- If you have dehydration.

- If you have kidney disease/increased or decreased kidney functioning.
- In newborn babies with jaundice (yellowing of the skin or eyes) or Rh incompatibility.
- If you are pregnant or breastfeeding.

Before using LASIX SPECIAL, tell your health provider if you have any of the following conditions so he can carefully consider the risks and benefits of a treatment with LASIX SPECIAL:

- Any liver disease
- Urinary retention (difficulty to urinate)

What the medicinal ingredient is:

Furosemide

What the nonmedicinal ingredients are:

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

What dosage forms it comes in:

Tablets of 500 mg

WARNINGS AND PRECAUTIONS

LASIX SPECIAL IS A VERY STRONG WATER PILL WHICH IF GIVEN IN EXCESSIVE AMOUNTS CAN LEAD TO A PROFOUND WATER AND ELECTROLYTE LOSS FROM THE BODY. THEREFORE, CAREFUL MEDICAL SUPERVISION IS REQUIRED. THE DOSE AND DOSE SCHEDULE HAVE TO BE ADJUSTED TO THE INDIVIDUAL PATIENT'S NEEDS. BEFORE you use LASIX SPECIAL, talk to your health provider if:

- You have decreased blood pressure.
- You have liver disease or disorder.
- You have kidney disease or disorder.
- It is suspected you might be diabetic (high blood sugar).
- You have decreased ability to pass urine.
- You had an organ transplant.
- You have gout.
- You have lupus or had a medical history of an episode of lupus.
- You have been told by the doctor that you suffer from a narrowing of the arteries that supply your heart or brain.
- You have recently suffered from excess vomiting or diarrhea.
- You intend to have a surgery and general

IMPORTANT: PLEASE READ

anesthesia (even at the dentist's office), as there may be a sudden fall in blood pressure associated with general anesthesia.

- You are breast feeding, pregnant, or think you might be pregnant.
- You intend to change your eating habits.
- You are less than 16 years old.
- You are older than 61 years old.

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

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

The administration of LASIX SPECIAL to diabetic patients may result in possible decrease of diabetic control. Dosage adjustments of the antidiabetic agent may be needed. There have been cases of ringing in the ears, reversible and non-reversible deafness especially in children. This is most true when the patient has severe kidney disease or is taking drugs that are known to sometimes damage the ears while they are taking LASIX SPECIAL. Your doctor will decide if LASIX SPECIAL is the right medication for you based on your particular condition.

LASIX SPECIAL 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. Treatment during pregnancy requires monitoring of fetal growth by your doctor.

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

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

INTERACTIONS WITH THIS MEDICATION

Before using LASIX SPECIAL, tell your health provider about medication you are currently taking.

This way appropriate adjustment and decision can be taken for your treatment with LASIX SPECIAL.

Below are drugs or drug classes that may interact with LASIX SPECIAL. These include:

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

IMPORTANT: PLEASE READ

PROPER USE OF THIS MEDICATION

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

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

Usual dose:

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

Your doctor will prescribe LASIX SPECIAL at an individualized dose, based on your condition.

Maximum daily dose: 1000 mg.

Take the tablets without chewing with a glass of water.

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

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

Overdose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its beneficial effects, LASIX SPECIAL like all other drugs may sometimes cause undesirable effects. These may include: blurring of vision, constipation, diarrhea, dizziness, dry mouth, fatigue, tachycardia, arrhythmia (heart rhythm disturbance),

feeling of pressure in the head, increase in the amount and frequency of your urine, leg cramps, mental confusion, nausea, sweating, thirst, vomiting, hepatic encephalopathy (altered mental state due to liver disease). Talk to your doctor or pharmacist if you experience any of the above.

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

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

Symptom / effect	Talk with your doctor or pharmacist immediately		Stop taking drug and seek immediate medical attention
	Only if severe	In all cases	
Hearing problems; deafness, sometimes non-reversible		✓	
Fever, sore throat, fatigue, lesions in the mouth or on the lips			✓
Skin rash and/or blistering			✓
Hives and/or itching			✓
Abdominal pain		✓	
Difficulty to urinate			✓
Low blood pressure (hypotension): dizziness when rising to a standing position, impaired concentration and lightheadedness		✓	
Yellow coloration of the skin (jaundice)			✓
Dehydration and/or abnormal blood tests: dryness of the mouth, thirst, weakness, dizziness, fainting or loss of consciousness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, racing or irregular heartbeats, nausea and vomiting, sweating, increases in blood sugar levels, increased urination, mental confusion, headache			✓

IMPORTANT: PLEASE READ

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

Symptom / effect	Talk with your doctor or pharmacist immediately		Stop taking drug and seek immediate medical attention
	Only if severe	In all cases	
Muscle problems: unexplained muscle pain, tenderness, weakness, cramps		✓	
Pseudo –Bartter syndrome: abnormal blood tests, fatigue, muscle weakness, diarrhea, dehydration, increased thirst, increased urination, low blood pressure, irregular heartbeats			✓
Blurred vision		✓	
Allergic reactions: eyes sensitive to light, tingling of fingers or toes, fever			✓
Blood clots: pain, swelling tenderness in your leg or arm, warm, red skin and a heavy feeling in the affected area			✓
Failure of the kidneys: weakness, trouble breathing, swelling, fast or irregular heartbeat, confusion, decrease or inability to urinate, loss of appetite, coma and death			✓
In premature babies: discoloured urine and/or blood in the urine/diaper, fever and chills, vomiting, excessive crying or other signs the baby is in pain			✓
In premature babies: poor weight gain		✓	

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

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

HOW TO STORE IT

Store your tablets at room temperature (15° – 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 the doctor tells you to keep them at home.

As with all medicines, keep LASIX SPECIAL out of reach of children.

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.

MORE INFORMATION

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

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