LASIX® (furosemide) Tablets 20, 40, and 80 mg

Rx Only

WARNING
LASIX® (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule must be adjusted to the individual patient’s needs. (See DOSAGE AND ADMINISTRATION.)

DESCRIPTION
LASIX® is a diuretic which is an anionic acid derivative. LASIX tablets for oral administration contain furosemide as the active ingredient and the following inactive ingredients: lactose monohydrate NF, magnesium stearate NF, mannoglycerol NF, talc USP, and colloidal silicon dioxide NF. Formically, it is 4-chloro-N-[2-tert-butyloxycarbonylamino]phenyl-N-[2-(1-methylureido)ethyl] butane-1,2-dione. LASIX is available as white tablets for oral administration in dosage strengths of 20, 40 and 80 mg. Furosemide is a white to off-white odorless crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkaline solutions and insoluble in dilute acids. The CAS Registry Number is 54-31-9.

The structural formula is as follows:

![structual_formula]

CLINICAL PHARMACOLOGY
Investigations into the mode of action of LASIX have utilized micropuncture studies in rats, stop flow experiments in dogs and various clearance studies in both humans and experimental animals. It has been demonstrated that LASIX inhibits primarily the absorption of sodium and chloride not only in the proximal and distal tubules but also in the loop of Henle. The high degree of efficacy is largely due to the unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrate and aldosterone.

Recent evidence suggests that furosemide glucuronide is the only or at least the major biotransformation product of furosemide in man. Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations range from 1 to 40 µg/mL in healthy individuals. The unbound fraction averages 2.3 to 4.1% at therapeutic concentrations.

The onset of diuresis following oral administration is within 1 hour. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6 to 8 hours.

In fasted normal men, the mean bioavailability of furosemide from LASIX Tablets and LASIX Oral Solution is 64% and 60%, respectively, of that from an intravenous injection of the drug. Although furosemide is more rapidly absorbed from the oral solution (50 minutes) than from the tablet (87 minutes), peak plasma levels and area under the plasma concentration-time curves do not differ significantly. Peak plasma concentrations increase with increasing dose but times-to-peak do not differ among doses. The terminal half-life of furosemide is approximately 2 hours.

Significantly more furosemide is excreted in urine following the IV injection than after the tablet or oral solution. There are no significant differences between the two oral formulations in the amount of unchanged drug excreted in urine.

Geriatric Population
Furosemide binding to albumin may be reduced in elderly patients. Furosemide is predominantly excreted unchanged in the urine. The renal clearance of furosemide after intravenous administration in older healthy male subjects (60–70 years of age) is statistically significantly smaller than in younger healthy male subjects (20–35 years of age). The initial diuretic effect of furosemide in older subjects is decreased relative to younger subjects. (See PRECAUTIONS: Geriatric Use)

INDICATIONS AND USAGE
Edema
LASIX is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. LASIX is particularly useful when an agent with greater diuretic potential is desired.

Hypertension
Oral LASIX may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with LASIX alone.

CONTRAINDICATIONS
LASIX is contraindicated in patients with anuria and in patients with a history of hypersensitivity to furosemide.

WARNINGS
In patients with hepatic cirrhosis and ascites, LASIX therapy is best initiated in the hospital. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, LASIX should be discontinued.

Cases of fatal and reversible or irreversible hearing impairment and deafness have been reported. Reports usually indicate that LASIX ototoxicity is associated with rapid injection, severe renal impairment, the use of higher than recommended doses, hypopotassemia or concomitant therapy with aminoglycoside antibiotics, ethanolic acid, or other ototoxic drugs. If the physician elects to use high dose parenteral therapy, controlled intravenous infusion is advisable (for adults, an infusion rate not exceeding 4 mg per min LASIX per minute has been used). (See PRECAUTIONS: Drug Interactions)

PRECAUTIONS
General
Excessive diuresis may cause dehydration and blood volume reduction with circulatory collapse and potentially life-threatening thrombocytopenia, particularly in elderly patients. As with any effective diuretic, electrolyte depletion may occur during LASIX therapy, especially in patients receiving higher doses and a restricted salt intake. Hypokalemia may develop with LASIX, especially with brisk diuresis, inadequate oral electrolyte intake, when cirrhosis is present, or during concomitant use of corticos-
Literature reports indicate that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of LASIX (furosemide) in some patients by inhibiting prostaglandin synthesis. Indomethacin may also affect plasma renin levels, aldosterone excretion, and renin profile evaluation. Patients receiving both indomethacin and LASIX should be observed closely to determine if the desired diuretic and/or antihypertensive effect of LASIX is achieved.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Furosemide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats. A small but significantly increased incidence of mammary gland carcinomas occurred in female mice at a dose 17.5 times the maximum human dose of 600 mg. There were marginal increases in unconfirmed tumors in male rats at a dose of 15 mg/kg (slightly greater than the maximum human dose) but not at 30 mg/kg.

Furosemide was devoid of mutagenic activity in various strains of Salmonella typhimurium when tested in the presence or absence of an in vitro metabolic activation system, and questionably positive for gene mutation in mouse lymphoma cells in the presence of rat liver S9 at the highest dose tested. Furosemide did not induce sister chromatid exchange in human cells in vitro, but other studies on chromosomal aberrations in human cells in vitro gave conflicting results. In Chinese hamster cells it induced chromosomal damage but was questionably positive for sister chromatid exchange. Studies on the induction by furosemide of chromosomal aberrations in mice were inconclusive. The urine of rats treated with this drug did not induce gene conversion in Saccharomyces cerevisiae.

LASIX (furosemide) produced no impairment of fertility in male or female rats, at 100 mg/kg/day (the maximum effective diuretic dose in the rat and 8 times the maximal human dose of 600 mg/day).

Pregnancy

PREGNANCY CATEGORY C - Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the maximal recommended human dose. There are no adequate and well-controlled studies in pregnant women. LASIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Treatment during pregnancy requires monitoring of fetal growth because of the potential for higher birth weights.

The effects of furosemide on embryonic and fetal development and on pregnant dams were studied in mice, rats and rabbits. Furosemide caused unexplained maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg (2 times the maximal recommended human dose of 600 mg/day). In another study, a dose of 50 mg/kg (4 times the maximal recommended human dose of 600 mg/day) also caused maternal deaths and abortions when administered to rabbits between Days 12 and 17 of gestation. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality that can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence and severity of hydrenephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from the treated dams as compared with the incidence in fetuses from the control group.

Nursing Mothers

Because it appears in breast milk, caution should be exercised when LASIX is administered to a nursing mother.

LASIX may inhibit lactation.

Pediatric Use

In premature infants LASIX may precipitate nephrocalcinosis/nephrolithiasis. Nephrocalcinosis/nephrolithiasis has also been observed in children under 4 years of age with no history of prematurity who have been treated chronically with LASIX. Monitor renal function, and renal ultrasonography should be considered, in pediatric patients receiving LASIX.

If LASIX is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Geriatric Use

Controlled clinical studies of LASIX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for the elderly patient should be cautious, usually starting at the low end of the dosing range (see PRECAUTIONS: General and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Adverse reactions are categorized below by organ system and listed by decreasing severity.

Gastrointestinal System Reactions
1. hepatic encephalopathy in patients with hepatocellular insufficiency
2. pancreatitis
3. jaundice (intrathecal cholestatic jaundice)
4. increased liver enzymes
5. anorexia
6. oral and gastric irritation
7. cramping
8. diarrhea
9. constipation
10. nausea
11. vomiting

Systemic Hypersensitivity Reactions
1. Severe anaphylactic or anaphylactoid reactions (e.g. with shock)
2. systemic vasculitis
3. interstitial nephritis
4. necrotizing angiitis

Central Nervous System Reactions
1. tinnitus and hearing loss
2. paresthesia
3. vertigo
4. dizziness
5. headache
6. blurred vision
7. xanthopsia

Cardiovascular Reaction
The acute toxicity of LASIX has been determined in mice, rats and dogs. In all three, the oral LD50 exceeded 1000 mg/kg body weight, while the intravenous LD50 ranged from 300 to 600 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats.

OVERDOSAGE

The principal signs and symptoms of overdose with LASIX are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hyperchloremic alkalosis, and are extensions of its diuretic action.

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The concentration of LASIX in biological fluids associated with toxicity or death is not known.

Treatment of overdosage is supportive and consists of 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).

Hemodialysis does not accelerate furosemide elimination.

DOSAGE AND ADMINISTRATION

Edema

Therapy should be individualized according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response.

Adults

The usual initial dose of LASIX is 20 to 80 mg given as a single dose. Ordinarily a prompt diuresis ensues. If needed, the same dose can be administered 8 to 8 hours later or the dose may be increased.

The dose may be raised by 20 or 40 mg and given not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. The individually determined single dose should then be given once or twice daily (e.g., 8 am and 2 pm). The dose of LASIX may be carefully titrated up to 600 mg/day in patients with clinically severe edematous states.

Edema may be most efficiently and safely mobilized by giving LASIX on 2 to 4 consecutive days each week.

When doses exceeding 80 mg/day are given for prolonged periods, careful clinical observation and laboratory monitoring are particularly advisable. (See PRECAUTIONS: Laboratory Tests.) Geriatric patients

In general, dose selection for the elderly patient should be cautious, usually starting at the low end of the dosing range (see PRECAUTIONS: Geriatric Use).

Pediatric patients

The usual initial dose of LASIX in pediatric patients is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg no sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended. For maintenance therapy in pediatric patients, the dose should be adjusted to the minimum effective level.

Hypertension

Therapy should be individualized according to the patient's response to gain maximal therapeutic response and to determine the minimal dose needed to maintain the therapeutic response.

Adults

The usual initial dose of LASIX for hypertension is 80 mg, usually divided into 40 mg twice a day.

Dose selection should then be adjusted according to response. If response is not satisfactory, add one or more antihypertensive agents.

Changes in blood pressure must be carefully monitored when LASIX is used with other antihypertensive drugs, especially during initial therapy. To prevent excessive drop in blood pressure, the dosage of other agents should be reduced by at least 50 percent when LASIX is added to the regimen. As the blood pressure falls under the potentializing effect of LASIX, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

Geriatric patients

In general, dose selection and dose adjustment for the elderly patient should be cautious, usually starting at the low end of the dosing range (see PRECAUTIONS: Geriatric Use).
HOW SUPPLIED

LASIX (furosemide) Tablets 20 mg are supplied as white, oval, monogrammed tablets in Bottles of 100 (NDC 0039-0067-10), and 1000 (NDC 0039-0067-70). The 20 mg tablets are imprinted with “Lasix®” on one side.

LASIX Tablets 40 mg are supplied as white, round, monogrammed, scored tablets in Bottles of 100 (NDC 0039-0060-13), 500 (NDC 0039-0060-50), and 1000 (NDC 0039-0060-70). The 40 mg tablets are imprinted with “Lasix® 40” on one side.

LASIX Tablets 80 mg are supplied as white, round, monogrammed, facetted edge tablets in Bottles of 50 (NDC 0039-0066-05) and 500 (NDC 0039-0066-50). The 80 mg tablets are imprinted with “Lasix® 80” on one side.

Note: Dispense in well-closed, light-resistant containers. Exposure to light might cause a slight discoloration. Discolored tablets should not be dispensed.

 Tested by USP Dissolution Test 2

Store at 25° C (77° F); excursions permitted to 15 – 30° C (59 – 86° F). [See USP Controlled Room Temperature.]

Revised August 2011