FUROSEMIDE

(fur-*oh*-se-mide) Lasix®

LOOP DIURETIC

Prescriber Highlights

- A loop diuretic commonly used in many species for treatment of congestive cardiomyopathy, pulmonary edema, udder edema, hypercalcuric nephropathy, uremia, as adjunctive therapy in hyperkalemia &, occasionally, as an antihypertensive agent
- Used in racehorses to prevent/reduce EIPH
- Contraindications: Patients with anuria, hypersensitivity, or seriously depleted electrolytes
- Caution: Patients with pre-existing electrolyte or water balance abnormalities, impaired hepatic function, & diabetes mellitus
- Adverse Effects: Fluid & electrolyte (esp. hyponatremia) abnormalities, others included: ototoxicity, GI distress, hematologic effects, ototoxicity, weakness, & restlessness
- Pre-renal azotemia if dehydration occurs
- Encourage normal food & water intake

Uses/Indications

Furosemide is used for its diuretic activity in all species. It is used in small animals for the treatment of congestive cardiomyopathy, pulmonary edema, hypercalcuric nephropathy, uremia, as adjunctive therapy in hyperkalemia and, occasionally, as an antihypertensive agent. In cattle, it is approved for use for the treatment of post-parturient udder edema. It has been used to help prevent or reduce epistaxis (exercise-induced pulmonary hemorrhage; EIPH) in racehorses.

Pharmacology/Actions

Furosemide reduces the absorption of electrolytes in the ascending section of the loop of Henle, decreases the reabsorption of both sodium and chloride and increases the excretion of potassium in the distal renal tubule, and directly effects electrolyte transport in the proximal tubule. The exact mechanisms of furosemide's effects have not been fully established. It has no effect on carbonic anhydrase nor does it antagonize aldosterone.

Furosemide increases renal excretion of water, sodium, potassium, chloride, calcium, magnesium, hydrogen, ammonium, and bicarbonate. In dogs, excretion of potassium is affected much less so than is sodium; hyponatremia may be more of a concern than hypokalemia. It causes some renal venodilation and transiently increases glomerular filtration rates (GFR). Renal blood flow is increased and decreased peripheral resistance may occur. While furosemide increases renin secretion, due to its effects on the nephron, increases in sodium and water retention do not occur. Furosemide can cause hyperglycemia, but to a lesser extent than the thiazides.

At high doses (10–12 mg/kg), thoracic duct lymph flow is increased in dogs. In horses, guinea pigs and humans, furosemide has some bronchodilative effects. Cats are reportedly more sensitive than other species to the diuretic effects of furosemide.

Pharmacokinetics

The pharmacokinetics of furosemide have been studied in a limited fashion in domestic animals. In dogs, the oral bioavailability is approximately 77% and the elimination half-life approximately 1–1.5 hours.

In humans, furosemide is 60–75% absorbed following oral administration. The diuretic effect takes place within 5 minutes after IV administration and within one hour after oral dosing. Peak effects occur approximately 30 minutes after IV dosing, and 1–2 hours after oral dosing. The drug is approximately 95% bound to plasma proteins in both azotemic and normal patients. The serum half-life is about 2 hours, but prolonged in patients with renal failure, uremia, CHF, and in neonates.

Contraindications/Precautions/Warnings

Furosemide is contraindicated in patients with anuria or who are hypersensitive to the drug. The manufacturer states that the drug should be discontinued in patients with progressive renal disease if increasing azotemia and oliguria occur during therapy.

Furosemide should be used with caution in patients with preexisting electrolyte or water balance abnormalities, impaired hepatic function (may precipitate hepatic coma), and diabetes mellitus. Patients with conditions that may lead to electrolyte or water balance abnormalities (*e.g.*, vomiting, diarrhea, etc.) should be monitored carefully. Patients hypersensitive to sulfonamides may also be hypersensitive to furosemide (not documented in veterinary species).

Adverse Effects

Furosemide may induce fluid and electrolyte abnormalities. Patients should be monitored for hydration status and electrolyte imbalances (especially potassium, calcium, magnesium and sodium). Prerenal azotemia may result if moderate to severe dehydration occurs. Hyponatremia is probably the greatest concern, but hypocalcemia, hypokalemia, and hypomagnesemia may all occur. Animals that have normal food and water intake are much less likely to develop water and electrolyte imbalances than those who do not.

Other potential adverse effects include ototoxicity, especially in cats with high dose IV therapy. Dogs reportedly require dosages greater than 22 mg/kg IV to cause hearing loss. Other effects include gastrointestinal disturbances, hematologic effects (anemia, leukopenia), weakness, and restlessness.

Reproductive/Nursing Safety

In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.*)

Furosemide appears in milk; clinical significance to nursing offspring is unknown.

Overdosage/Acute Toxicity

The LD_{50} in dogs after oral administration is >1000 mg/kg; after IV injection >300 mg/kg. Chronic overdosing at 10 mg/kg for six months in dogs led to development of calcification and scarring of the renal parenchyma.

Acute overdosage may cause electrolyte and water balance problems, CNS effects (lethargy to coma and seizures) and cardiovascular collapse.

Treatment consists of emptying the gut after recent oral ingestion, using standard protocols. Avoid giving concomitant cathartics as they may exacerbate the fluid and electrolyte imbalances that can occur. Aggressively monitor and treat electrolyte and water balance abnormalities supportively. Additionally, monitor respiratory, CNS, and cardiovascular status. Treat supportively and symptomatically if necessary.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving furosemide and may be of significance in veterinary patients:

- **ACE INHIBITORS** (*e.g.*, **enalapril, benazepril**): Increased risks for hypotension, particularly in patients who are volume or sodium depleted secondary to diuretics
- **AMINOGLYCOSIDES** (**gentamicin, amikacin,** etc.): Increased risk for ototoxicity
- **AMPHOTERICIN B**: Loop diuretics may increase the risk for nephrotoxicity development; hypokalemia
- **CORTICOSTEROIDS**: Increased risk for GI ulceration; hypokalemia
- **DIGOXIN**: Furosemide-induced hypokalemia may increase the potential for digoxin toxicity
- **INSULIN**: Furosemide may alter insulin requirements
- **MUSCLE RELAXANTS, NON-DEPOLARIZING** (*e.g.*, **atracurium, tubocurarine**): Furosemide may prolong neuromuscular blockade
- **PROBENECID**: Furosemide can reduce uricosuric effects
- **SALICYLATES**: Loop diuretics can reduce the excretion of salicylates
- **SUCCINYLCHOLINE**: Furosemide may potentiate
- **THEOPHYLLINE**: Pharmacologic effects of theophylline may be enhanced when used with furosemide

Doses

- **DOGS & CATS:**

  As a general diuretic:

  a) 2.5–5 mg/kg (lower dose suggested for cats) once or twice daily at 6–8 hour intervals PO, IV or IM (Package Insert; *Salix*®—Intervet)

  For cardiogenic or pulmonary edema:

  a) For adjunctive therapy of CHF: 0.5–2 mg/kg PO per day. The goal is to find the lowest dose of furosemide that will prevent development of effusion or edema. This may change over time. (Ware and Keene 2000)

  b) For severe pulmonary edema (parenteral dosing)

  Dogs: Up to 7.7 mg/kg IV or IM every 1–2 hours until respiratory rate and/or respiratory character improves;

  Cats: Up to 4.4 mg/kg IV or IM every 1–2 hours until respiratory rate and/or respiratory character improves;

  For heart failure (oral dosing; often in combination with an ACE inhibitor and digoxin):

  Dogs: Dosage ranges from 1.1 mg/kg PO every other day for very mild heart failure to 4.4 mg/kg PO q8h for severe heart failure;

  Cats: Dosage ranges from 1.1 mg/kg PO every 2–3 days to 2.2 mg/kg, q8–12h. (May require doses up to 6.6. mg/kg q12h or 15.4 mg/kg PO once a day for cats that are difficult to treat orally).

  Animals must drink adequate amounts of water or severe dehydration may result (Kittleson 2000)

  c) The credo for furosemide therapy is: "Use as much as the case requires, and as little as necessary." Prior to therapy, obtain serum chemistry and full urinalysis (or at least measure urine specific gravity).

  For severe pulmonary edema (parenteral dosing):

  Dogs: Up to 8 mg/kg IV every hour with adjunctive therapy (usually strict cage rest, O_2 therapy, topical NTG ointment and minimal restraint) until improved.

  For chronic maintenance therapy: Usually start at 2 mg/kg PO q12h, but will adjust as necessary. Rarely go above 4 mg/kg PO q8h. If case requires more than this dosage, add hydrochlorothiazide at 2–4 mg/kg PO q12h. However, at this point prognosis is becoming dismal. Encourage oral food and water intake. (Tobias 2001)

  d) Using furosemide as a constant rate infusion (CRI): May dilute 5% injection (50 mg/mL) in D5W to a concentration of 5 mg/mL or 10 mg/mL without precipitation occurring; give as a CRI and titrate dose to between 0.1–1 mg/kg/hour. (Rush 2005a)

  For hypercalcemia/hypercalcuric nephropathy:

  a) For adjunctive treatment of moderate to severe hypercalcemia: Volume expansion is necessary prior to use of furosemide; 2–4 mg/kg two to three times daily, IV, SC or PO. (Chew, Schenck et al. 2003)

  For acute oliguric renal failure:

  a) Initially 2 mg/kg IV; if no substantial diuresis develops in one hour, the dose may be doubled to 4 mg/kg. If this dose fails to induce diuresis, may increase to 6 mg/kg. If diuresis still does not ensue, very large doses of furosemide, an alternative diuretic (*e.g.*, mannitol), or the combination of furosemide and dopamine may be considered. (Polzin 2005a)

  To promote diuresis in hyperkalemic states:

  a) 2 mg/kg IV; attempted if mannitol is ineffective after one hour (Seeler and Thurmon 1985)

  As a diuretic for the treatment of ascites:

  a) 1–2 mg/kg PO, SC once to twice daily (Morgan 1988)

- **FERRETS:**

  For adjunctive therapy for heart failure:

  a) 2–3 mg/kg IM or IV initially for fulminant CHF; 1–2 mg/kg PO q12h for long-term maintenance therapy (Hoeffer 2000)

  b) 1–4 mg/kg PO, SC, IM or IV 2–3 times a day (Williams 2000)

- **RABBITS/RODENTS/SMALL MAMMALS:**

  a) Rabbits: For CHF: 2–5 mg/kg PO, SC, IM or IV q12h; For pulmonary edema: 1–4 mg/kg IV or IM q4–6h (Ivey and Morrisey 2000)

  b) Mice, Rats, Gerbils, Hamsters, Guinea pigs, Chinchillas: 5–10 mg/kg q12h (Adamcak and Otten 2000)

- **CATTLE:**

  a) 500 mg once daily or 250 mg twice daily; 2 grams PO once daily. Treatment not to exceed 48 hours post-partum (for udder edema). Package Insert; *Lasix*®–Hoechst)

  b) 2.2–4.4 mg/kg IV q12h (Howard 1986)

- **HORSES:**

  (**Note:** Refer to state guidelines for use of furosemide in racing animals)

  As a diuretic:

  a) For adjunctive therapy for congestive heart failure: Initially, 1–2 mg/kg IM or IV q6–12h to control edema. Long-term therapy: 0.5–2 mg/kg PO or IM q8–12h (Mogg 1999)

  b) For adjunctive therapy of acute renal failure: 2–4 mg/kg q6h (Jose-Cunilleras and Hinchcliff 1999)

For epistaxis prevention:

a) 0.3–0.6 mg/kg 60–90 minutes prior to race (Robinson 1987)

b) 250 mg IV 4 hours prior to racing (Foreman 1999)

- **BIRDS:**

As a diuretic:

a) 0.05 mg/300 gm IM twice daily (**Note**: Lories are very sensitive to this agent and can be easily overdosed) (Clubb 1986)

- **REPTILES:**

For most species:

a) 5 mg/kg IV or IM as needed (Gauvin 1993)

Monitoring

- Serum electrolytes, BUN, creatinine, glucose
- Hydration status
- Blood pressure, if indicated
- Clinical signs of edema, patient weight, if indicated
- Evaluation of ototoxicity, particularly with prolonged therapy or in cats

Client Information

- Clients should contact veterinarian if clinical signs of water or electrolyte imbalance occur, such as excessive thirst, lethargy, lassitude, restlessness, reduced urination, GI distress or fast heart rate.

Chemistry/Synonyms

A loop diuretic related structurally to the sulfonamides, furosemide occurs as an odorless, practically tasteless, white to slightly yellow, fine, crystalline powder. Furosemide has a melting point between 203°–205°C with decomposition, and a pK_a of 3.9. It is practically insoluble in water, sparingly soluble in alcohol, and freely soluble in alkaline hydroxides. The injectable product has its pH adjusted to 8–9.3 with sodium hydroxide.

Furosemide may also be known as: frusemide, furosemidum, and LB-502; many trade names are available.

Storage/Stability/Compatibility

Furosemide tablets should be stored in light-resistant, well-closed containers. The oral solution should be stored at room temperature and protected from light and freezing. Furosemide injection should be stored at room temperature. A precipitate may form if the injection is refrigerated, but will resolubolize when warmed without alteration in potency. The human injection (10 mg/mL) should not be used if it has a yellow color. The veterinary injection (50 mg/mL) normally has a slight yellow color. Furosemide is unstable at an acid pH, but is very stable under alkaline conditions.

Furosemide injection (10 mg/mL) is reportedly physically **compatible** with all commonly used intravenous solutions and the following drugs: amikacin sulfate, cimetidine HCl, kanamycin sulfate, tobramycin sulfate, and verapamil.

It is reportedly physically **incompatible** with the following agents: ascorbic acid solutions, dobutamine HCl, epinephrine, gentamicin sulfate, netilmicin sulfate and tetracyclines. It should generally not be mixed with antihistamines, local anesthetics, alkaloids, hypnotics, or opiates.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Furosemide Tablets: 12.5 mg, 50 mg; *Salix*® (Intervet); *Disal*® *Tablets* (Boehringer Ingelheim), *Furotabs*® (Butler); generic (Phoenix Pharmaceutical); (Rx). Products may be approved for use in dogs and cats.

Furosemide Oral Solution (Syrup): 10 mg/mL in 60 mL; generic (IVX, First Priority); (Rx) Approved for use in dogs.

Furosemide for Injection: 50 mg/mL (5%) in 50 mL and 100 mL vials; *Disal*® *Injection* (Boehringer Ingelheim), *Salix*® *Injection* (Intervet), *Furoject*® (Butler), generic (AgriLabs, IVX, Vet Tek, Phoenix Pharmaceutical), (Rx). Products may be approved for use in dogs, cats and horses.

HUMAN-LABELED PRODUCTS:

Furosemide Tablets: 20 mg, 40 mg, & 80 mg; *Lasix*® (Aventis); generic; (Rx)

Furosemide Oral Solution: 10 mg/mL in 60 mL and 120 mL; 40 mg/5 mL in 500 mL and UD 5 mL and 10 mL; generic; (Rx)

Furosemide Injection: 10 mg/mL in 2 mL, 4 mL and 10 mL single-dose vials and 10 mL multi-dose vial; generic; (Rx)

GABAPENTIN

(gab-ah-***pen***-tin) Neurontin®

ANTICONVULSANT; NEUROPATHIC PAIN ANALGESIC

Prescriber Highlights

- **May be useful in dogs & cats as adjunctive therapy for refractory or complex partial seizures or the treatment of pain**
- **Caution in patients with diminished renal function, but dogs partially (30–40%) metabolize the drug (humans do not)**
- **Avoid use of xylitol-containing oral liquid in dogs**
- **Sedation most likely adverse effect, but adverse effect profile not well-defined for animals**
- **Expense may be a significant issue, but may decrease as generics are now available**

Uses/Indications

Gabapentin may be useful as adjunctive therapy for refractory or complex partial seizures, or in the treatment of chronic pain in dogs or cats.

Pharmacology/Actions

Gabapentin has analgesic effects and can prevent allodynia (sensation of pain resulting from a normally non-noxious stimulus) or hyperalgesia (exaggerated response to painful stimuli). It also has anticonvulsant activity. The mechanism of action of gabapentin, for either its anticonvulsant or analgesic actions is not understood. While gabapentin is structurally related to GABA, it does not appear to alter GABA binding, reuptake, or degradation, or serve as a GABA agonist *in vivo*.

Pharmacokinetics

In dogs, oral bioavailability is about 80% at a dose of 50 mg/kg. Peak plasma levels occur about 2 hours post dose. Elimination is primarily via renal routes, but gabapentin is partially metabolized to N-methyl-gabapentin. Elimination half-life is approximately 2–4 hours in dogs. No pharmacokinetic data for cats was located.

In humans, gabapentin bioavailability decreases as dosage increases. At doses of 900 mg/day, 60% of the dose is absorbed. Percentage absorbed is reduced as doses are increased to a minimum of 27%