

Date of Approval: NOV 18 2005

**FREEDOM OF INFORMATION (FOI) SUMMARY**

**ORIGINAL ABBREVIATED NEW ANIMAL DRUG  
APPLICATION**

**ANADA 200-373**

**Furosemide Syrup 1%  
(furosemide)**

**Oral Diuretic, Saluretic**

**A diuretic-saluretic for oral use alone or in combination with Furosemide Injection in the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema.**

**Sponsored by:**

**First Priority, Inc.**

## FREEDOM OF INFORMATION SUMMARY

### 1. GENERAL INFORMATION:

- a. File Number: ANADA 200-373
- b. Sponsor: First Priority, Inc.  
1585 Todd Farm Dr.  
Elgin, IL 60123
- Drug Labeler Code: 058829
- c. Established Name: Furosemide
- d. Proprietary Name: Furosemide Syrup 1%
- e. Dosage Form: Syrup
- f. How Supplied: 60 mL bottles
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: 10 mg of furosemide per mL
- i. Route of Administration: Oral
- j. Species/Class: Dogs
- k. Recommended Dosage: Dog: 1 to 2 mL (10-20 mg) Furosemide Syrup 1% for each 10 lb. body weight. Administer once or twice daily at 6 to 8 hour intervals. Dispense in this container with calibrated safety dropper. Use dropper to measure and administer Furosemide Syrup 1%.
- l. Pharmacological Category: Diuretic
- m. Indications: A diuretic-saluretic for oral use alone or in combination with Furosemide Injection in the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema.
- n. Pioneer Product: LASIX (furosemide) Syrup 1%;  
NADA 102-380; Intervet, Inc.

## **2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:**

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Ordinarily the ANADA Sponsor shows the generic product is bioequivalent to the pioneer, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from the requirement of an *in vivo* bioequivalence study (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 2000).

Based on the formulation characteristics of the generic product, First Priority, Inc. was granted a waiver from the requirement for an *in vivo* bioequivalence study for the generic product Furosemide Syrup 1%. The generic product is administered as an oral solution and contains the same active ingredient in the same concentration and dosage form as the pioneer product. The generic product contains no inactive ingredients that may significantly affect the absorption of the active ingredient. The pioneer product LASIX (furosemide) Syrup 1%; the subject of Intervet, Inc. NADA 102-380, was approved on March 17, 1998.

## **3. HUMAN SAFETY:**

This drug is indicated only for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this ANADA.

Human warning statements are provided on the product labeling as follows: **“Keep out of the reach of children.”**, and **“FOR USE IN DOGS ONLY.”**

## **4. AGENCY CONCLUSIONS:**

This ANADA filed under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that Furosemide Syrup 1%, when used under its proposed conditions of use, is safe and effective for its labeled indications.

**5. ATTACHMENTS:**

Facsimile generic labeling and currently approved pioneer labeling are attached as indicated below:

Generic Labeling for ANADA 200-373:

Furosemide Syrup 1%, 60 mL label with calibrated safety dropper

Furosemide Syrup 1%, Package Insert

Furosemide Syrup 1%, Carton Printing

Pioneer Labeling for NADA 102-380:

LASIX (furosemide) Syrup 1%, 60 mL label with calibrated safety dropper

LASIX (furosemide) Syrup 1%, Package Insert

LASIX (furosemide) Syrup 1%, Carton Printing

000003

A diuretic-saluretic for oral use alone or in combination with Lasix® (furosemide) Injection in the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema.

**DIRECTIONS:**

**DOG:** 1 to 2 mL (10-20 mg) Lasix® Syrup 1% for each 10 lb. body weight. Administer once or twice daily at 6- to 8-hour intervals. Dispense in this container with calibrated safety dropper. Use dropper to measure and administer Lasix® Syrup. See insert for full prescribing information.

**NDC 12799-194-06**

**60 mL**

**FOR USE IN DOGS ONLY**

**Lasix®**  
**(furosemide)**

**Syrup 1%**  
**(10 mg/mL)**

**with calibrated safety dropper**

**Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

419406-6/96

Literature

Literature

Distribution

Labeling

050004



Exp:  
Lot:

Lasix® (furosemide)  
Syrup 1% (10 mg/mL)

**CAUTIONS:**  
Keep container tightly closed.  
Discard opened bottle after 60  
days. Protect from light.

This product contains alcohol  
11.5% USP as a preservative,  
and FD&C Yellow #6 and D&C  
Yellow #10 as color additives.

Store at controlled room tem-  
perature (59 to 86° F).  
Keep this and all medication  
out of the reach of children.

Lasix REG TM HOECHST AG

Manufactured by:  
**HOECHST-ROUSSEL**  
Pharmaceuticals  
Division of Hoechst Marion  
Roussel, Inc.  
Kansas City, MO 64137

Distributed by:  
**HOECHST ROUSSEL Vet**  
Somerville, NJ 08876-1258

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The name and logo Hoechst are  
registered trademarks of Hoechst AG



**NDC 12799-194-06**



**60 mL**

**FOR USE IN DOGS ONLY**

**Lasix®**  
**(furosemide)**

**Syrup 1%**  
**(10 mg/mL)**

**with calibrated safety dropper**

**Caution:** Federal law restricts this drug to use  
by or on the order of a licensed veterinarian.

000005

A diuretic-saline for oral use alone or in combination with Lasix® (furosemide) injection in the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory laryngitis.

Caution: Keep container tightly closed. Discard opened bottle after 60 days. Protect from light. Store at controlled room temperature (59 to 86°F).

Lasix REG TM  
LOT: \_\_\_\_\_  
EXP: \_\_\_\_\_  
HOECHST AG

NDC 12739-194-06  
60 mL  
FOR USE IN DOGS ONLY

**Lasix®**  
(furosemide)

Syrup 1%  
(10 mg/mL)

with calibrated safety dropper

Keep this and all medication out of the reach of children. Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**DIRECTIONS:**  
DOG: 1 to 2 mL (10-20 mg) Lasix® (furosemide) Syrup 1% for each 10 lb. body weight. Administer once or twice daily at 8- to 9-hour intervals. Dispense in this container with calibrated safety dropper. Use dropper to measure and administer Lasix® Syrup. See insert for full prescribing information. This product contains alcohol 11.5% USP as a preservative, and FD&C Yellow #6 and D&C Yellow #10 as color additives.

Manufactured by  
HOECHST-ROUSSEL Pharmaceuticals  
Division of Hoechst Marion Roussel, Inc.  
Kansas City, MO 64137

**Hoechst** 

Distributed by  
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A member of the Hoechst Group  
Somerville, NJ 08876-1254

**DO NOT USE AFTER**  
DATE: \_\_\_\_\_



019406-098

**Oral:**

Lasix® Tablets 50 mg (scored) and 12.5 mg, available in bottles of 500.  
Lasix® Syrup 1% (10 mg/mL), available in 60 mL bottles with calibrated safety dropper.

**TOXICOLOGY****Acute Toxicity:**

The following table illustrates low acute toxicity of Lasix® in three different species  
(Two values indicated two different studies.)

LD<sub>50</sub> of Lasix®  
in mg/kg body weight

SPECIES	ORAL	INTRAVENOUS
Mouse	1050-1500	308
Rat	2650-4600*	680
Dog	>1000 and >4640	>300 and >484

NOTE: The lower oral LD<sub>50</sub> value for the rat was obtained in a group of fasted animals; the higher figure is from a study performed on fed rats.  
Toxic doses lead to convulsions, ataxia, paralysis and collapse. Animals surviving toxic doses may become dehydrated and depleted of electrolytes due to the massive diuresis and saluresis.

**Chronic Toxicity:**

Chronic toxicity studies with Lasix® were done in a one-year study in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred with all doses higher than 50 mg/kg. A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg.

**Reproductive Studies:**

Reproductive studies were conducted in mice, rats and rabbits. Only in rabbits administered high doses (equivalent to 10 to 25 times the recommended average dose of 10 mg/kg for dogs, horses and cattle) of furosemide during second trimester did unexplained maternal deaths and abortions occur. Lasix® (furosemide) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The effects of alcohol administered to pregnant Beagles at 3 and at 3.6 gms/kg/day throughout gestation suggests that alcohol may reduce number of offspring per litter, the birth weight per pup increase the incidence of stillbirths. There have been no studies conducted in pregnant dogs administered alcohol at levels found in Lasix® 1% Syrup.

**REFERENCES**

1. Timmerman RJ, Springman FR, Thomas RK: Evaluation of furosemide, a new diuretic agent. *Curr Ther Res* 6:88-94, 1964.
2. Muschawek R, Hajdu P: The saluretic action of 4-Chloro-N-(2-furylmethyl)-5-sulfamyl-anthranilic acid. (Die salidiuretische Wirksamkeit der Chlor-N-(2-furylmethyl)-5-sulfamyl-anthranilsäure.) *Arzneim Forsch* 14:44-47, 1964.
3. Suki W, Rector FC Jr, Seldin DW: The site of action of furosemide and other sulfonamide diuretics in the dog. *J Clin Invest* 44:1458-1469, 1965.
4. Deatjen P: Micropuncture studies of the action of furosemide. (Mikropunktionsuntersuchungen zur Wirkung von Furosemid.) *Pluegers Arch* 284:184-190, 1965.
5. Berman LB, Ebrahimi A: Experiences with furosemide in renal disease. *Proc Soc Exp Biol Med* 118:333-338, 1965.
6. Schmidt HAE: Animal experiments with S35 tagged Lasix® in canine and ovine. Internal report, Radiochemical Pharmacological Laboratory, Frankfurt West Germany, Farbwerke Hoechst, 1964.
7. Haessler A, Hajdu P: Methods of biological identification and results of studies on absorption, elimination, and metabolism. Internal report, Research Laboratories, Frankfurt, West Germany, Farbwerke Hoechst.
8. Wilson AF, Simmons DH: Diuretic action in hypochloremic dogs. *Clin Res* 14:158, 1966.
9. Hook JB, Williamson HE: Influence of probenecid and alterations and acid-base balance of the saluretic activity of furosemide. *J Pharmacol Exp Ther* 149:404-408, 1965.
10. Antoniou LD, et al: Sodium and calcium transport in the kidney. *Clin Res* 15:478, 1967.
11. Duarte CG: Effects of furosemide (F) and ethacrynic acid (ETA) on the renal clearance of phosphate (Cp), ultra-filterable calcium (CU-Ca) and magnesium (CU-Mg) *Clin Res* 15:357, 1967.
12. Duarte CG: Effects of ethacrynic acid and

furosemide on urinary calcium, phosphate and magnesium. *Metabolism* 17:867-876, 1968.

13. Nielsen SP, Andersen O, Steven KE, Magnesium and calcium metabolism during prolonged furosemide (Lasix®) administration to normal rats. *Acta Pharmacol Toxicol* 27:469-479, 1969.
14. Reimold EW: The effect of furosemide on hypercalcemia due to dihydrotachysterol. *Metabolism* 21:593-598, 1972.

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trademarks of Hoechst AG

719400-6/96

719400-6/96

FOR USE IN DOGS ONLY

# Lasix®

(furosemide)

Syrup 1%

A diuretic-saluretic for prompt relief of edema.

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION**

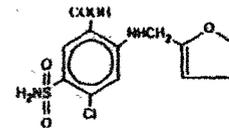
Lasix® (furosemide) is a chemically distinct diuretic and saluretic pharmacodynamically characterized by the following:

- 1) A high degree of efficacy, low-inherent toxicity and a high therapeutic index.
- 2) A rapid onset of action of comparatively short duration. 1,2
- 3) A pharmacologic action in the functional area of the nephron, i.e., proximal and distal tubules and the ascending limb of the loop of Henle. 2-4
- 4) A dose-response relationship and a ratio of minimum to maximum effective dose range greater than ten fold. 1,2
- 5) It may be administered orally or parenterally. It is readily absorbed from the intestinal tract and well tolerated. The intravenous route produces the most rapid diuretic response.

The CAS Registry Number is: 54-31-9.

This product contains alcohol 11.5% USP as a preservative, and FD&C Yellow #6 and D&C Yellow #10 as color additives.

Lasix®, a diuretic, is an anthranilic acid derivative with the following structural formula:



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Generic name: Furosemide (except in United Kingdom — frusemide).

Chemical name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

#### ACTIONS

The therapeutic efficacy of Lasix® (furosemide) is from the activity of the intact and unaltered molecule throughout the nephron, inhibiting the reabsorption of sodium not only in the proximal and distal tubule, but also in the ascending limb of the loop of Henle. The prompt onset of action is a result of the drug's rapid absorption and a poor lipid solubility. The low lipid solubility and a rapid renal excretion minimizes the possibility of lipid accumulation in tissues and organs or of crystalluria. Lasix® has no inhibitory effect on carbonic anhydrase or aldosterone activity in the distal tubule. The drug possesses diuretic activity in the presence of either acidosis or alkalosis. 1-7

#### INDICATIONS

##### DOG

Lasix® is an effective diuretic possessing a wide therapeutic range. Pharmacologically it promotes the rapid removal of abnormally retained extracellular fluids. The rationale for the efficacious use of diuretic therapy is determined by the clinical pathology producing the edema.

Lasix® is indicated for the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema. The continued use of heart stimulants, such as digitalis or its glycosides, is indicated in cases of edema involving cardiac insufficiency.

#### CONTRAINDICATIONS-PRECAUTIONS

Lasix® is a highly effective diuretic-saluretic which if given in excessive amounts may result in dehydration and electrolyte imbalance. Therefore, the dosage and schedule may have to be adjusted to the patients' needs. The animal should be observed for early signs of electrolyte imbalance, and corrective measures administered. Early signs of electrolyte imbalance are: increased thirst, lethargy, drowsiness or restlessness, fatigue, oliguria, gastrointestinal disturbances and tachycardia. Special attention should be given to potassium levels.

Lasix® may lower serum calcium levels and cause tetany in rare cases of animals having an existing hypocalcemic tendency. 10-14

Although diabetes mellitus is a rarely reported disease in animals, active or latent diabetes mellitus may on rare occasions be exacerbated by Lasix® (furosemide).

While it has not been reported in animals, the use of high doses of salicylates, as in rheumatic diseases, in conjunction with Lasix® may result in salicylate toxicity because of competition for renal excretory sites.

Electrolyte balance should be monitored prior to surgery in patients receiving Lasix® (furosemide). Imbalances must be corrected by administration of suitable fluid therapy.

Lasix® is contraindicated in anuria. Therapy should be discontinued in cases of progressive renal disease if increasing azotemia and oliguria occur during the treatment. Sudden alterations of fluid and electrolyte imbalance in an animal with cirrhosis may precipitate hepatic coma; therefore, observation during period of therapy is necessary. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Potassium supplementation may be necessary in cases routinely treated with potassium depleting steroids.

#### WARNINGS

Lasix® is a highly effective diuretic and, as with any diuretic, if given in excessive amounts may lead to excessive diuresis that could result in electrolyte imbalance, dehydration and reduction of plasma volume, enhancing the risk of circulatory collapse, thromboembolism, and embolism. Therefore, the animal should be observed for early signs of fluid depletion with electrolyte imbalance, and corrective measures administered. Excessive loss of potassium in patients receiving digitalis or its glycosides may precipitate digitalis toxicity. Caution should be exercised in animals administered potassium-depleting steroids.

It is important to correct potassium deficiency with dietary supplementation. Caution should be exercised in prescribing enteric-coated potassium tablets.

There have been several reports in human literature, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with non-enteric-coated thiazides, or certain other oral diuretics. These small-bowel lesions may have caused obstruction, hemorrhage, and perfora-

tion. Surgery was frequently required, and deaths have occurred. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distension, nausea, vomiting, or gastrointestinal bleeding occurs.

Human patients with known sulfonamide sensitivity may show allergic reactions to Lasix® (furosemide); however, these reactions have not been reported in animals.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix® and it is advisable to discontinue Lasix® for one day prior to any elective surgery.

#### DOSAGE AND ADMINISTRATION

The usual dose of Lasix® is 1 to 2 mg/lb. body weight (approximately 2.5 to 5 mg/kg). Administer once or twice daily at 6- to 8-hour intervals either orally, intravenously, or intramuscularly. A prompt diuresis usually ensues from the initial treatment. Diuresis may be initiated by the parenteral administration of Lasix® (furosemide) injection and then maintained by oral administration.

The dosage should be adjusted to the individual's response. In severe edematous or refractory cases, the dose may be doubled or increased by increments of 1 mg/lb. body weight. The established effective dose should be administered once or twice daily. The daily schedule of administration can be timed to control the period of micturition of the convenience of the client or veterinarian. Mobilization of the edema may be most efficiently and safely accomplished by utilizing an intermittent daily dosage schedule, i.e., every other day or 2 to 4 consecutive days weekly.

Diuretic therapy should be discontinued after reduction of the edema, or maintained after determining a carefully programmed dosage schedule to prevent recurrence of edema. For long-term treatment, the dose can generally be lowered after the edema has once been reduced. Re-examination and consultations with client will enhance the establishment of a satisfactorily programmed dosage schedule. Clinical examination and serum BUN, CO<sub>2</sub> and electrolyte determinations should be performed during the early period of therapy and periodically thereafter, especially in refractory cases. Abnormalities should be corrected or the drug temporarily withdrawn.

#### DOSAGE

##### ORAL:

##### DOG

##### Syrup 1%

One to 2 mL (10 to 20 mg furosemide) per 10 lb. body weight (approximately 2.5 to 5 mg/kg)

Administered once or twice daily, permitting a 6- to 8-hour interval between treatments. In refractory or severe edematous cases, the dosage may be doubled or increased by increments of 1 mg/lb. body weight as recommended in preceding paragraphs. "DOSAGE AND ADMINISTRATION"

##### DOG & CAT

Tablets (12.5 mg and 50 mg)

One Lasix® (furosemide) 12.5 mg tablet per 5 to 10 lb. body weight. Administer once or twice daily at 6 to 8 hour intervals.

One Lasix® 50 mg scored tablet per 25 to 50 lb. body weight. Administer once or twice daily at 6 to 8 hour intervals.

The 12.5 mg or 50 mg tablet may be doubled or increased by increments of 1 mg/lb. body weight in refractory or severe edema cases.

##### PARENTERAL:

##### DOG

Administer intramuscularly or intravenously 1/4 to 1/2 mL per 10 lb. body weight (approximately 2.5 to 5 mg/kg).

Administer once or twice daily, permitting a 6- to 8-hour interval between treatments. In refractory or severe edematous cases the dosage may be doubled or increased by increments of 1 mg/lb. body weight as recommended in preceding paragraphs. "DOSAGE AND ADMINISTRATION"

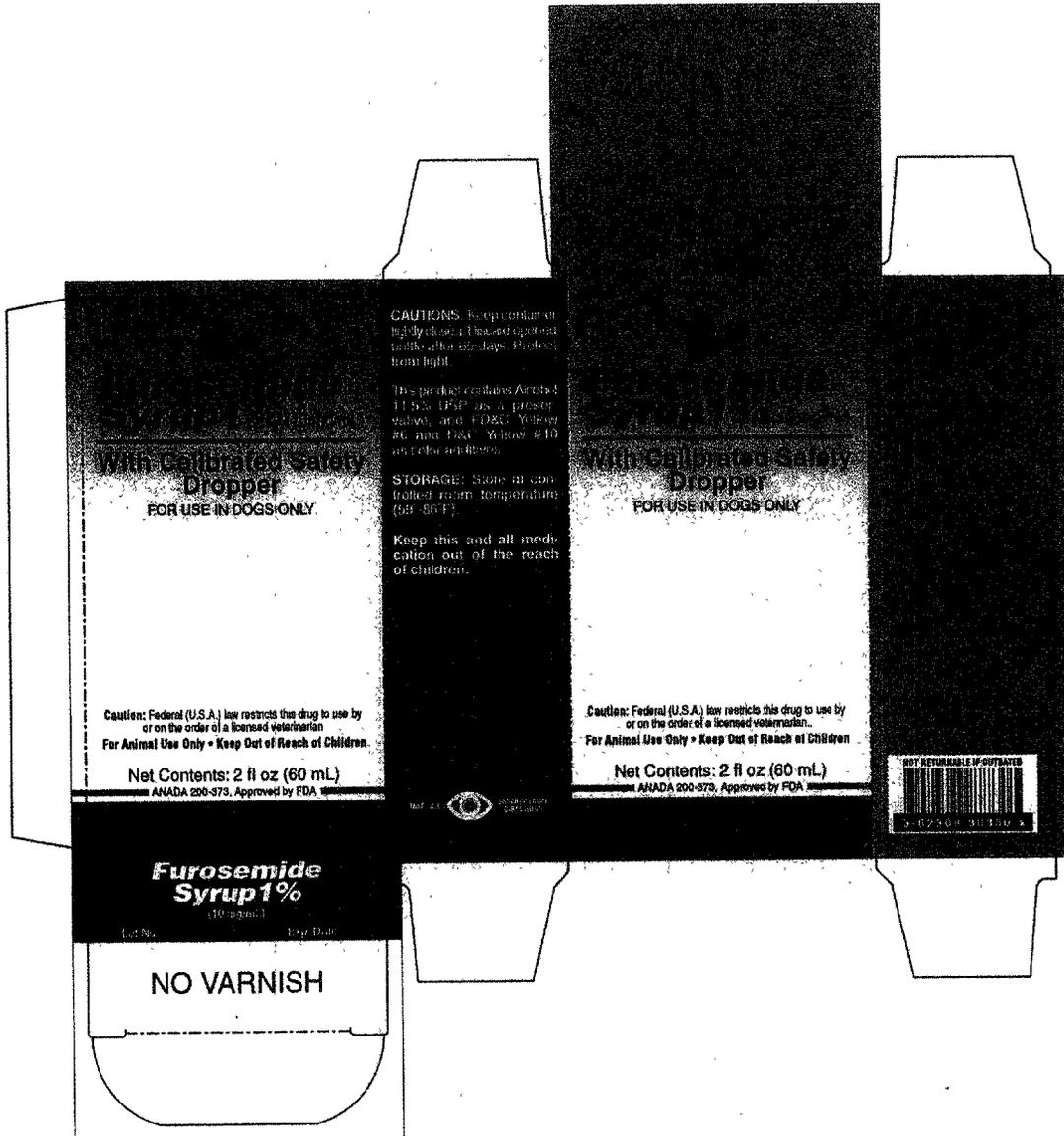
#### HOW SUPPLIED

##### Parenteral:

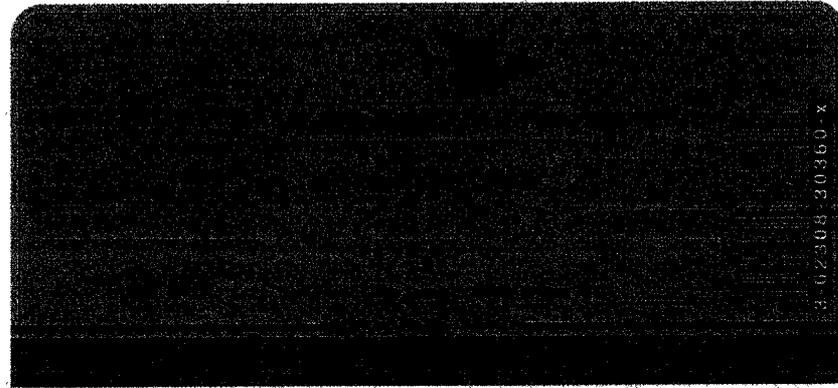
Lasix® (furosemide) injection 5% (50 mg/mL)

Each mL contains: 50 mg furosemide as diethanolamine salt preserved and stabilized with myristyl-gamma-picolinium chloride 0.02%, EDTA sodium 0.1%, sodium sulfite 0.1% with sodium chloride 0.2% in distilled water, pH adjusted with sodium hydroxide. Available in 50 mL multikose vials.

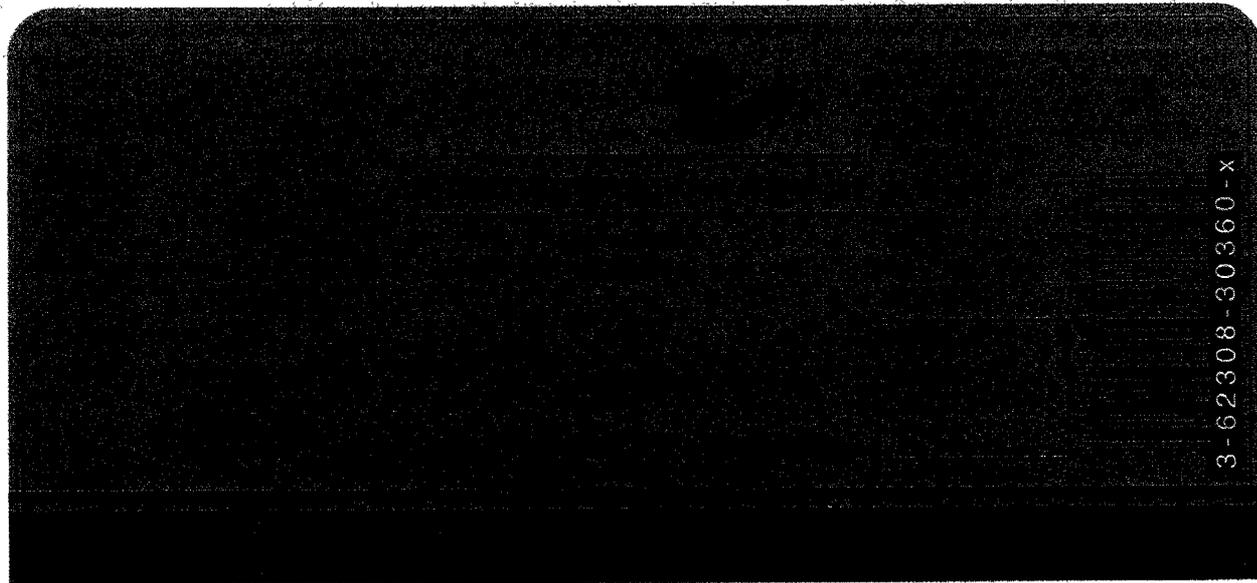
**DRAFT**  
For Comp Only



Actual Label Size  
2 x 4.5



150% of actual size



## Furosemide Syrup 1%

(10 mg/mL)

### FOR USE IN DOGS ONLY

A diuretic-saluretic for prompt relief of edema

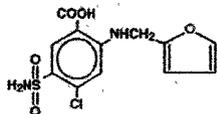
Caution: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian

**DESCRIPTION:** Furosemide Syrup 1% is a chemically distinct diuretic and saluretic pharmacodynamically characterized by the following:

- 1) A high degree of efficacy, low inherent toxicity and a high therapeutic index.
- 2) A rapid onset of action of comparatively short duration, 1-2
- 3) A pharmacologic action in the functional area of the nephron, i.e., proximal and distal tubules and the ascending limb of the loop Henle, 2-4
- 4) A dose-response relationship and a ratio of minimum to maximum effective dose range greater than ten fold, 1,2
- 5) It is administered orally. It is readily absorbed from the intestinal tract and well tolerated.

The CAS Registry Number is: 54-31-9

This product contains alcohol 11.5% USP as a preservative, and FD&C Yellow #6 and D&C Yellow #10 as color additives. Furosemide Syrup 1%, a diuretic, is an anthranilic acid derivative with the following structural formula.



Generic name: Furosemide (except in United Kingdom-furosemide). Chemical name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

#### ACTIONS

The therapeutic efficacy of Furosemide Syrup 1% is from the activity of the intact and unaltered molecule throughout the nephron, inhibiting the reabsorption of sodium not only in the proximal and distal tubule, but also in the ascending limb of the loop of Henle. The prompt onset of action is a result of the drug's rapid absorption and a poor lipid solubility

The low lipid solubility and a rapid renal excretion minimizes the possibility of lipid accumulation in tissues and organs or of crystalluria. Furosemide Syrup 1% has no inhibitory effect on carbonic anhydrase or aldosterone activity in the distal tubule. The drug possesses diuretic activity in the presence of either acidosis or alkalosis. 1-7

#### INDICATIONS

##### DOG

Furosemide Syrup 1% is an effective diuretic possessing a wide therapeutic range. Pharmacologically it promotes the rapid removal of abnormally retained extracellular fluids. The rationale for the efficacious use of diuretic therapy is determined by the clinical pathology producing the edema. Furosemide Syrup 1% is indicated for the treatment of edema (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema. The continued use of heart stimulants, such as digitalis or its glycosides, is indicated in cases of edema involving cardiac insufficiency.

1

#### CONTRAINDICATION-PRECAUTIONS

Furosemide Syrup 1% is a highly effective diuretic-saluretic which if given in excessive amounts may result in dehydration and electrolyte imbalance. Therefore, the dosage and schedule may have to be adjusted to the patient's needs. The animal should be observed for early signs of electrolyte imbalance, and corrective measures administered. Early signs of electrolyte imbalance are: increased thirst, lethargy, drowsiness or restlessness, fatigue, oliguria, gastrointestinal disturbances and tachycardia. Special attention should be given to potassium levels.

Furosemide Syrup 1% may lower serum calcium levels and cause tetany in rare cases of animals having an existing hypocalcemic tendency, 10-14. Although diabetes mellitus is a rarely reported disease in animals, active or latent diabetes mellitus may on rare occasions be exacerbated by Furosemide Syrup 1%. While it has not been reported in animals, the use of high doses of salicylates, as in rheumatic diseases, in conjunction with Furosemide Syrup 1% may result in salicylate toxicity because of competition for renal excretory sites. Electrolyte balance should be monitored prior to surgery in patients receiving Furosemide Syrup 1%. Imbalances must be corrected by administration of suitable fluid therapy.

Furosemide Syrup 1% is contraindicated in anuria. Therapy should be discontinued in cases of progressive renal disease if increasing azotemia and oliguria occur during the treatment. Sudden alterations of fluid and electrolyte imbalance in an animal with cirrhosis may precipitate hepatic coma; therefore, observation during therapy is necessary. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected.

Potassium supplementation may be necessary in cases routinely treated with potassium depleting steroids.

#### WARNINGS

Furosemide Syrup 1% is a highly effective diuretic and, as with any diuretic, if given in excessive amounts may lead to excessive diuresis that could result in electrolyte imbalance, dehydration and reduction of plasma volume, enhancing the risk of circulatory collapse, thrombosis, and embolism. Therefore, the animal should be observed for early signs of fluid depletion with electrolyte imbalance, and corrective measures administered. Excessive loss of potassium in patients receiving digitalis or its glycosides may precipitate digitalis toxicity. Caution should be exercised in animals administered potassium-depleting steroids. It is important to correct potassium deficiency with dietary supplementation. Caution should be exercised in prescribing enteric-coated potassium tablets.

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2

decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Furosemide Syrup 1% and it is advisable to discontinue Furosemide Syrup 1% for one day prior to any elective surgery.

#### DOSEAGE AND ADMINISTRATION

The usual dose of Furosemide Syrup 1% is 1 to 2 mg/lb body weight (approximately 2.5 to 5 mg/kg). Administer once or twice daily at 6- to 8-hour intervals orally. A prompt diuresis usually ensues from the initial treatment. Diuresis may be initiated by the parenteral administration of furosemide injection and then maintained by oral administration. The dosage should be adjusted to the individual's response. In severe edematous or refractory cases, the dose may be doubled or increased by increments of 1 mg/lb body weight. The established effective dose should be administered once or twice daily. The daily schedule of administration can be timed to control the period of micturition of the convenience of the client or veterinarian. Mobilization of the edema may be most efficiently and safely accomplished by utilizing an intermittent daily dosage schedule, i.e., every other day or 2 to 4 consecutive days weekly. Diuretic therapy should be discontinued after reduction of the edema, or maintained after determining a carefully programmed dosage schedule to prevent recurrence of edema. For long-term treatment, the dose can generally be lowered after the edema has once been reduced. Re-examination and consultations with client will enhance the establishment of a satisfactorily programmed dosage schedule. Clinical examination and serum BUN, CO<sub>2</sub> and electrolyte determinations should be performed during the early period of therapy and periodically thereafter, especially in refractory cases. Abnormalities should be corrected or the drug temporarily withdrawn.

#### DOSEAGE

##### ORAL:

##### DOG-Syrup 1%

One (1) to two (2) mL (10 to 20 mg furosemide) per 10 lb body weight (approximately 2.5 to 5 mg/kg). Administered once or twice daily, permitting a 6- to 8-hour interval between treatments.

In refractory or severe edematous cases, the dosage may be doubled or increased by increments of 1 mg/lb body weight as recommended in preceding paragraphs, "DOSEAGE AND ADMINISTRATION."

#### HOW SUPPLIED

##### Oral:

Furosemide Syrup 1% (10 mg/mL), available in 60 mL bottles with calibrated safety dropper.

#### TOXICOLOGY

##### Acute Toxicity:

The following table illustrates low acute toxicity of Furosemide Syrup 1% in three different species. (Two values indicated two different studies).

##### LD50 of Furosemide Syrup 1% in mg/kg body weight

SPECIES	ORAL	INTRAVENOUS
Mouse	1050-1500	308
Rat	2650-4600*	680
Dog	>1000 and >4640	>300 and >464

\*NOTE: The lower oral LD50 value for the rat was obtained in a group of fasted animals, the higher figure is from a study performed on fed rats.

Toxic doses lead to convulsions, ataxia, paralysis and collapse. Animals surviving toxic doses may become dehydrated and depleted of electrolytes due to the massive diuresis and saluresis.

##### Chronic Toxicity:

Chronic toxicity studies with Furosemide Syrup 1% were done in a one-year study in rats and dogs. In a one-year

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study in rats, renal tubular degeneration occurred with all doses higher than 50 mg/kg. A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg.

#### Reproductive Studies:

Reproductive studies were conducted in mice, rats and rabbits. Only in rabbits administered high doses (equivalent to 10 to 25 times the recommended average dose of 2 mg/kg for dogs, horses and cattle) of furosemide during the second trimester did unexplained maternal deaths and abortions occur. Furosemide Syrup 1% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The effects of alcohol administered to pregnant Beagles at 3 and at 3.6 gms/kg/day throughout gestation suggests that alcohol may reduce the number of offspring per litter, the birth weight per pup and increase the incidence of stillbirths. There have been no studies conducted in pregnant dogs administered alcohol at levels found in Furosemide Syrup 1%.

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