Date of Approval: July 18, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION (ANADA)

ANADA 200-759

Furosemide Tablets

Dogs and Cats

Furosemide Tablets are 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 Tablets are 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.

Sponsored by:

ZyVet Animal Health, Inc.

Executive Summary

Furosemide Tablets are approved as 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 Tablets are 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. The reference listed new animal drug (RLNAD) is Salix® (furosemide tablets), sponsored by Intervet, Inc., under NADA 034-621. This is the first generic furosemide tablet for dogs and cats.

Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 50 mg Furosemide Tablet is bioequivalent to the 50 mg Salix® tablet. No serious adverse events were reported during the study. The sponsor also conducted one *in vivo* blood-level study in cats to show that the 12.5 mg Furosemide Tablet is bioequivalent to the 12.5 mg Salix® tablet. No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strengths, 12.5 mg for dogs and 50 mg for cats. Based on the dissolution data, the 12.5 mg tablet qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver) in dogs and 50 mg tablet qualified for a waiver from the requirement to perform separate biowaiver studies in cats. FDA granted a biowaiver for these strengths.

Conclusions

Based on the data submitted by the sponsor for the approval of Furosemide Tablets, FDA determined that the drug is safe and effective when used according to the label.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-759

B. Sponsor

ZyVet Animal Health, Inc.
73 Route 31N
Pennington, NJ 08534

Drug Labeler Code: 086117

C. Proprietary Name

Furosemide Tablets

D. Drug Product Established Name

furosemide tablets

E. Pharmacological Category

Diuretic, saluretic

F. Dosage Form

Tablet

G. Amount of Active Ingredient

12.5 mg or 50 mg furosemide/tablet

H. How Supplied

12.5 mg or 50 mg tablets in 500 count containers

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The usual dosage of furosemide is 1 to 2 mg/lb body weight (approximately 2.5 to 5 mg/kg). The lower dosage is suggested for cats. 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 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 per pound 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 for 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.

K. Route of Administration

Oral

L. Species/Classes

Dogs and Cats

M. Indications

Furosemide Tablets are 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 Tablets are 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.

N. Reference Listed New Animal Drug

Salix®; furosemide tablets; NADA 034-621; Intervet, Inc.

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug (RLNAD). The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is demonstrated through a clinical endpoint study in a food-producing animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the 50 mg generic and RLNAD furosemide tablets in dogs, and the 12.5 mg generic and RLNAD tablets in cats. The RLNAD is available in 12.5 and 50 mg tablet strengths. The *in vivo* blood-level study in dogs was conducted in 28 healthy, fasted beagle dogs and the *in vivo* blood-level study in cats was conducted in 28 healthy, male neutered cats. The pivotal parameters to evaluate bioequivalence are the observed maximum plasma drug concentration (C_{MAX}) and area under the concentration-time curve (AUC) from time 0 to the last sampling time before the first unquantifiable concentration after C_{MAX}.

Bioequivalence was demonstrated between the 12.5 mg RLNAD furosemide tablets and the 12.5 mg generic furosemide tablets in cats and the 50 mg RLNAD furosemide tablets and the 50 mg generic furosemide tablets in dogs using the mixed reference-scaled average bioequivalence approach. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 12.5 mg tablets in dogs and the generic 50 mg tablets in cats was requested. Dissolution data was used to demonstrate that the 12.5 mg generic and the 12.5 mg RLNAD furosemide tablets were comparable, and the 50 mg generic and the 50 mg RLNAD furosemide tablets were comparable, and the generic 12.5 mg furosemide tablets were comparable to the generic 50 mg furosemide tablets. Therefore, a biowaiver for the generic 12.5 mg furosemide tablets in dogs and the 50 mg furosemide tablets in cats was granted. The study information is summarized below.

A. Blood-level Bioequivalence Study in Cats

Title: A Masked, Balanced, Randomized, Four-Period, Two-Sequence, Single-Dose Oral, Crossover Bioequivalence Study of Furosemide Tablets (12.5 Mg) and Salix® Tablets (12.5 Mg) In Healthy Cats Under Fasted Conditions. (Study No. 113-BF-2620)

Study Dates: April 26, 2022 to November 24, 2022

Study Locations:

In-life phase: Ontario, Canada

Bioanalytical testing: Ontario, Canada

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 12.5 mg furosemide tablet and the RLNAD 12.5 mg Salix® (furosemide tablets) in fasted cats.

Study Animals: 28 healthy neutered male cats between 1.5 and 2.5 years of age.

Experimental Design: A randomized, masked, four-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 12.5 mg of either the generic or RLNAD furosemide tablets according to their randomized treatment sequence (generic/RLNAD/generic/RLNAD or RLNAD/generic/RLNAD/generic).

Measurements and Observations: The plasma concentrations of furosemide were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

The laboratory study was conducted as a randomized, masked, four-period, two-sequence, two-treatment, single-dose crossover design using 28 cats with a 7-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

The mixed reference-scaled average bioequivalence approach (RSABE) was used to evaluate bioequivalence. Prior to the analysis, C_{MAX} and AUC values were natural logarithm transformed. The estimated within-subject standard deviation (s_{WR}) of the RLNAD was calculated separately for transformed C_{MAX} and AUC to select the appropriate analysis approach based on FDA Guidances.

- The s_{WR} was equal to or greater than 0.294 for both C_{MAX} and AUC, so the RSABE method was used and bioequivalence was established based on the following two criteria:
    - The estimated 95% upper confidence bound for $(\mu_T\text{-}\mu_R)^2\text{-}\ \theta^*\sigma^2_{WR}$ is less than zero (0), where μ_T and μ_R are the population means of the natural log transformed primary variable for the generic article and RLNAD, respectively, $\theta = (\log(1.25)/\sigma_{W0})^2$ and $\sigma_{W0} = 0.25$.
    - The point estimate of the generic to RLNAD geometric mean ratio is contained within the acceptance limits of 0.80 and 1.25.

Results:

As seen in the table below, C_{MAX} and AUC met the pre-specified criteria for bioequivalence (Table II.1). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.1. Bioequivalence Evaluation

Parameter	S_{WR}	Generic Mean	RLNAD Mean	Ratio[◊]	95% Upper Bound[$]
AUC (ng/mL)*hour	0.3130	5544.71[†]	6108.89[†]	0.91	-0.03
C_{MAX} (ng/mL)	0.5817	1056.17[†]	1214.40[†]	0.87	-0.12
T_{MAX} (hours) (SD)[‡]	NE	3.00 (1.92)[‡]	2.74 (1.77)[‡]	NE	NE

[†] Geometric mean
[‡] Arithmetic mean and standard deviation (SD)
[◊] Ratio = Generic/RLNAD
[$] 95% upper confidence bound for $(\mu_T\text{-}\mu_R)^2\text{-}\ \theta^*\sigma^2_{WR}$
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 12.5 mg furosemide tablet and the RLNAD 12.5 mg Salix® (furosemide tablets) are bioequivalent in cats.

B. Blood-level Bioequivalence Study in Dogs

Title: A Masked, Balanced, Randomized, Four-Period, Two-Sequence, Single-Dose Oral, Crossover Bioequivalence Study of Furosemide Tablet 50 mg and Salix® Tablet 50 mg in Healthy Adult Dogs Under Fasting Conditions. (Study No. 20C505Q1G197)

Study Dates: November 15, 2021 to January 13, 2023

Study Locations:

In-life phase: San Diego, California

Bioanalytical testing: Ontario, Canada

Study Design:

Objective: The objective of this study was to determine the comparative *in vivo* blood-level bioequivalence data for the generic 50 mg furosemide tablets and the RLNAD 50 mg Salix® (furosemide tablets) in fasted healthy adult male beagle dogs.

Study Animals: 28 healthy, intact male beagle dogs between 1.6 to 2.3 years of age and weighing 8.6 to 12.4 kg.

Experimental Design: A randomized, masked, four-period, two-sequence, single-dose crossover study conducted according to Good Laboratory Practice for Nonclinical Laboratory Studies.

Drug Administration: Each animal received 50 mg of either the generic or RLNAD furosemide tablets according to their randomized treatment sequence (generic/RLNAD/generic/RLNAD or RLNAD/generic/RLNAD/generic).

Measurements and Observations: The plasma concentrations of furosemide were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events.

Statistical Methods:

The laboratory study was conducted as a randomized, masked. four-period, two-sequence, two-treatment, single-dose crossover design using 28 dogs with an 8-day washout between periods. Appropriate randomization of animal to sequence and pen/treatment order was performed. Primary variables evaluated were C_{MAX} and AUC. Time to maximum concentration (T_{MAX}) was summarized and evaluated clinically.

The reference-scaled average bioequivalence (RSABE) was used as appropriate to evaluate bioequivalence through the mixed scaling approach. Prior to the analysis, C_{MAX} and AUC values were natural logarithm transformed. The estimated within-subject standard deviation (s_{WR}) of the RLNAD was calculated separately for transformed C_{MAX} and AUC to select the appropriate analysis approach based on FDA Guidances.

- The s_{WR} was less than 0.294 for AUC, so the average bioequivalence method was used to evaluate bioequivalence. The statistical model included fixed effects of treatment, sequence and period, and a random effect of subject nested within sequence. Period was modeled as a repeated factor. Bioequivalence was established because the back-transformed estimated upper and lower bounds of the pertinent 90% confidence interval for geometric mean ratios (generic:RLNAD) were contained within the acceptance limits of 0.80 to 1.25.

- The s_{WR} was equal to or greater than 0.294 for C_{MAX}, so the RSABE method was used and bioequivalence was established based on the following two criteria:

    - The estimated 95% upper confidence bound for $(\mu_T-\mu_R)^2- \theta^*\sigma^2_{WR}$ is less than zero (0), where μ_T and μ_R are the population means of the natural log transformed primary variable for the generic article and RLNAD, respectively, $\theta = (\log (1.25)/\sigma_{W0})^2$ and $\sigma_{W0} = 0.25$.

    - The point estimate of the generic to RLNAD geometric mean ratio is contained within the acceptance limits of 0.80 and 1.25.

Results:

As seen in the table below, C_{MAX} and AUC met the pre-specified criteria for bioequivalence (Table II.2). The mean values of T_{MAX} obtained for the generic article and RLNAD were summarized.

Table II.2. Bioequivalence Evaluation

Parameter	S_{WR}	Generic Mean	RLNAD Mean	Ratio[◊]	95% Upper Bound[$]	90% CI for the Ratio
AUC (ng/mL) *hour	0.157	5268[†]	5273[†]	1.00	NE	(0.95, 1.05)
C_{MAX} (ng/mL)	0.307	2265[†]	2571[†]	0.89	-0.011	NE
T_{MAX} (hours) (SD)[‡]	NE	0.91 (0.41)[‡]	1.02 (0.50)[‡]	NE	NE	NE

[†] Geometric mean
[‡] Arithmetic mean and standard deviation (SD)
[◊] Ratio = Generic/RLNAD
[$] 95% upper confidence bound for $(\mu_T-\mu_R)^2 - \theta^*\sigma^2_{WR}$
CI = confidence interval
NE = not estimated

Adverse Reactions:

There were no serious adverse events reported during the study.

Conclusion:

The *in vivo* bioequivalence study demonstrated that the generic 50 mg furosemide tablets and the RLNAD 50 mg Salix® (furosemide tablets) are bioequivalent in dogs.

C. Bioequivalence Waiver

Two pivotal *in vivo* blood bioequivalence studies were conducted using the 12.5 mg furosemide tablet strength in cats and the 50 mg furosemide tablet strength in dogs. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 50 mg tablets in cats and the generic 12.5 mg tablets in dogs was requested. To qualify for a biowaiver for each of these product strengths, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of the generic 12.5 mg and 50 mg furosemide tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 12.5 mg and generic 50 mg tablets
- Generic 12.5 mg and RLNAD 12.5 mg tablets
- Generic 50 mg and RLNAD 50 mg tablets

The objective was to satisfy f_2 criteria between the generic 12.5 mg tablet strength and the generic 50 mg tablet strength, or between the generic 12.5 mg tablet strength and the RLNAD 12.5 mg tablet strength and the generic 50 mg tablet strength and the RLAND 50 mg tablet strength.
Test conditions were as follows:

- Dissolution apparatus: USP Apparatus II
- Dissolution medium: Phosphate buffer, pH 5.8
- Dissolution medium volume: 900 mL
- Temperature: 37 ± 0.5 °C
- Paddle speed: 65 rpm
- Number of vessels: 12
- Data points: 10, 15, 20, 30, 45, and 60 minutes

The generic drug lot numbers used in the *in vivo* bioequivalence studies were the same lot used to support the *in vitro* profile comparisons. Analytical method validation was required to ensure that the quantification of drug concentrations in all samples was accurate and precise.

To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 10 and 15 minutes) should not be more than 20%, and at other time points should not be more than 10%. The percent coefficient of variation for all generic product profiles was within acceptable limits. Only one measurement should be considered after 85% dissolution of both of the products. The similarity factor (f_2) should be greater than 50 to ensure sameness or equivalence of two profiles.

CVM estimated f_2 metrics based on mean data, and a summary of the results is presented in Table II.3 below:

Table II.3. Similarity Results

Dissolution Comparison	Similarity Results
12.5 mg generic to the 50 mg generic	89.4
12.5 mg generic to the 12.5 mg RLNAD	54.6
50 mg generic to the 50 mg RLNAD	56.7

Study results demonstrate similar dissolution profiles for one within-product comparisons (generic 12.5 mg to generic 50 mg strength) and two between-product comparisons (generic 12.5 mg to RLNAD 12.5 mg strength, and generic 50 mg to RLNAD 50 mg strength). Therefore, a biowaiver for the generic 12.5 mg furosemide tablets in dogs and the generic 50 mg furosemide tablets in cats is granted.

III. HUMAN FOOD SAFETY

This drug is intended for use in dogs and cats. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this ANADA.

IV. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Furosemide Tablets:

Not for use in humans. Keep out of reach of children.

Human patients with known sulfonamide sensitivity may show allergic reactions to Furosemide Tablets; however, these reactions have not been reported in animals.

V. AGENCY CONCLUSIONS

The data submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that Furosemide Tablets, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.