Date of Approval: June 11, 2024

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-787

Phenylpropanolamine Hydrochloride

Chewable Tablet

Dogs

Phenylpropanolamine Hydrochloride is indicated for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

Sponsored by:

ZyVet Animal Health, Inc.

## Executive Summary

Phenylpropanolamine Hydrochloride chewable tablets are approved for the control of urinary incontinence due to urethral sphincter hypotonus in dogs. The reference listed new animal drug (RLNAD) is PROIN® (phenylpropanolamine hydrochloride) chewable tablets, sponsored by Pegasus Laboratories, Inc., under NADA 141-324. This is the first generic phenylpropanolamine hydrochloride chewable tablets for dogs.

## Bioequivalence

The sponsor conducted one *in vivo* blood-level study in dogs to show that the 25 mg Phenylpropanolamine Hydrochloride chewable tablets are bioequivalent to the 25 mg PROIN® chewable tablets. No serious adverse events were reported during the study.

The sponsor conducted a comparative *in vitro* dissolution study for the additional product strengths. Based on the dissolution data, the 50 and 75 mg chewable tablets qualified for a waiver from the requirement to perform separate *in vivo* bioequivalence studies (a biowaiver). U.S. Food and Drug Administration (FDA) granted a biowaiver for these strengths.

## Conclusion

Based on the data submitted by the sponsor for the approval of Phenylpropanolamine Hydrochloride chewable 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 200-787

## B. Sponsor

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

Drug Labeler Code: 086117

## C. Proprietary Name

Phenylpropanolamine Hydrochloride

## D. Drug Product Established Name

phenylpropanolamine hydrochloride

## E. Pharmacological Category

Sympathomimetic amine

## F. Dosage Form

Chewable tablet

## G. Amount of Active Ingredient

25, 50, or 75 mg phenylpropanolamine hydrochloride per tablet

## H. How Supplied

60 and 180 count bottles

## I. Dispensing Status

Prescription (Rx)

## J. Dosage Regimen

The total recommended dosage for oral administration is 2 mg/kg (0.91 mg/lb) of body weight twice daily. Phenylpropanolamine Hydrochloride is scored and dosage should be calculated in half-tablet increments.

## K. Route of Administration

Oral

## L. Species/Class

Dogs

### M. Indication

Phenylpropanolamine Hydrochloride is indicated for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

### N. Reference Listed New Animal Drug

PROIN®; phenylpropanolamine hydrochloride; NADA 141-324; Pegasus Laboratories, 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, one *in vivo* blood-level study was conducted to demonstrate product bioequivalence using the generic and RLNAD phenylpropanolamine hydrochloride 25 mg chewable tablets. The RLNAD is available in 25, 50, and 75 mg chewable tablet sizes. The *in vivo* blood-level study was conducted in 30 healthy, fasted beagle dogs. 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 25 mg PROIN® (phenylpropanolamine hydrochloride) chewable tablets and the 25 mg generic phenylpropanolamine hydrochloride chewable tablets by the average bioequivalence approach as described in the Statistical Methods section below. A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 50 mg and 75 mg chewable tablets was requested. Dissolution data was used to demonstrate that the generic 50 mg and 75 mg phenylpropanolamine hydrochloride chewable tablets are comparable to the generic 25 mg chewable tablet strength used in the *in vivo* blood-level bioequivalence study. Therefore, a biowaiver for the generic 50 mg and 75 mg phenylpropanolamine hydrochloride chewable tablets was granted. The study information is summarized below.

### A. Blood-level Bioequivalence Study in Dogs

**Title**: A Masked, Randomized, Three Period, Two Sequence, Single Oral Dose Crossover Pivotal Bioequivalence Study of Generic Phenylpropanolamine Hydrochloride Chewable Tablets (25 mg) versus PROIN® (phenylpropanolamine hydrochloride) Chewable Tablets (25 mg) in Healthy Dogs, Under Fasted Conditions. (Study No. 113-BC-1921)

**Study Dates:** April 11, 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 25 mg Phenylpropanolamine Hydrochloride chewable tablets and the RLNAD 25 mg PROIN® (phenylpropanolamine hydrochloride) chewable tablets in fasted dogs.

Study Animals: Thirty male intact beagle dogs between 1.25 and 3.5 years of age and weighing 10.4 to 12.2 kg.

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

Drug Administration: Each animal received 25 mg of either the generic or RLNAD phenylpropanolamine hydrochloride according to their randomized treatment sequence (generic/RLNAD/generic or RLNAD/generic/RLNAD).

Measurements and Observations: The plasma concentrations of phenylpropanolamine 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, three-period, two-sequence, two-treatment, single-dose crossover design using 30 dogs with a 7-day washout between periods 1 and 2, and a 14-day washout period between periods 2 and 3. 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.

A mixed-effect model was used to evaluate bioequivalence. The model included fixed effects of treatment, sequence and period, a random effect of subject nested within sequence, and a repeated factor of period with group=treatment and subject=animal in the repeated statement. Prior to the analysis, $C_{MAX}$ and AUC were natural logarithm transformed. Bioequivalence is established because the back-transformed estimated upper and lower bounds of the 90 percent confidence interval for geometric mean ratios (generic:RLNAD) of both $C_{MAX}$ and AUC are contained within the acceptance limits of 0.80 to 1.25.

**Results:**

As seen in the table below, $C_{MAX}$ and AUC fall within the prescribed bounds (Table II.1). The mean values of $T_{MAX}$ obtained for the generic article and RLNAD were summarized.

**Table II.1. Bioequivalence Evaluation**

| Parameter | Generic Mean | RLNAD Mean | Ratio◊ | Lower 90% CI | Upper 90% CI |
|---|---|---|---|---|---|
| AUC (ng/mL)*hour | 4133† | 4137† | 99.9 | 95.9 | 104.1 |
| $C_{MAX}$ (ng/mL) | 658† | 609† | 108.1 | 102.9 | 113.5 |
| $T_{MAX}$ (hours) (SD)‡ | 1.47 (0.46)‡ | 1.49 (0.51)‡ | NE | NE | NE |

† Geometric mean
‡ Arithmetic mean and standard deviation (SD)
◊ Ratio = Test/Reference
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 25 mg Phenylpropanolamine Hydrochloride chewable tablets and the RLNAD 25 mg PROIN® (phenylpropanolamine hydrochloride) chewable tablets are bioequivalent in dogs.

## B. Bioequivalence Waiver

A pivotal *in vivo* blood bioequivalence study was conducted using the 25 mg phenylpropanolamine hydrochloride chewable tablet strength. A biowaiver for the generic 50 mg and 75 mg chewable tablets 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 25 mg, 50 mg, and 75 mg phenylpropanolamine hydrochloride chewable tablets. The similarity factor ($f_2$) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 25 mg and generic 50 mg tablets
- Generic 25 mg and generic 75 mg tablets

The objective was to satisfy $f_2$ criteria between the generic 25 mg chewable tablet strength and the generic 50 mg and 75 mg chewable tablet strengths.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus I
- Dissolution medium: Phosphate buffer, pH 6.8
- Dissolution medium volume: 900 mL
- Temperature: 37°C ± 0.5°C
- Paddle speed: 100 rpm

- Number of vessels: 12
- Data points: 5, 10, 15, 20, 30, 45, and 60 minutes

The generic drug lot number used in the *in vivo* bioequivalence study was 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., 15 minutes) should not be more than 20 percent, and at other time points should not be more than 10 percent. The percent coefficient of variation for all generic product profiles was within acceptable limits. Only one measurement should be considered after 85 percent dissolution of one of the products. The $f_2$ should be greater than 50 to ensure sameness or equivalence of two profiles.

The Center for Veterinary Medicine (CVM) estimated $f_2$ metrics based on mean data, and a summary of the results is presented in table II.2 below:

**Table II.2. Similarity Results**

| Dissolution Comparison | Similarity Results |
|---|---|
| 25 mg generic to the 50 mg generic | 82.2 |
| 25 mg generic to the 75 mg generic | 66.3 |

Study results demonstrate similar dissolution profiles for all comparisons. Therefore, a biowaiver for the generic 50 mg and 75 mg phenylpropanolamine hydrochloride chewable tablets is granted.

## III. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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 Phenylpropanolamine Hydrochloride:

**Warnings:** Not for human use. Keep out of reach of children. Consult a physician in case of accidental ingestion by humans.

## 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 Phenylpropanolamine Hydrochloride, when used according to the label, is safe and effective for the conditions of use in the General Information Section above.