Date of Approval: August 4, 2011

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-324

PROIN Chewable Tablets

Phenylpropanolamine hydrochloride
Dogs

For the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

Sponsored by:

Pegasus Laboratories, Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-324
B. Sponsor:	Pegasus Laboratories, Inc. 8809 Ely Rd. Pensacola, FL 32514 Drug Labeler Code: 055246
C. Proprietary Name(s):	PROIN Chewable Tablets
D. Established Name(s):	phenylpropanolamine hydrochloride
E. Pharmacological Category:	Sympathomimetic amine
F. Dosage Form(s):	Scored chewable tablets
G. Amount of Active Ingredient(s):	25, 50, or 75 mg phenylpropanolamine, as hydrochloride, per tablet
H. How Supplied:	25 and 50 mg tablets are packaged in bottles containing 60 or 180 tablets and 75 mg tablets are packaged in bottles containing 60 tablets.
I. How Dispensed:	Rx
J. Dosage(s):	The total recommended dosage for oral administration is 2 mg/kg (0.91 mg/lb) of body weight twice daily. The dosage should be calculated in half-tablet increments.
K. Route(s) of Administration:	Oral
L. Species/Class(es):	Dogs
M. Indication(s):	PROIN is indicated for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

II. EFFECTIVENESS:

A. Dosage Characterization:

The goal of therapy with phenylpropanolamine hydrochloride (PPA) is to treat urinary incontinence in dogs due to urethral sphincter hypotonus while minimizing the potential for adverse events. Several case reports and dosing regimens have been described for the use of PPA to treat incontinence[1,2,3,4,5]. However, only a few published reports test the use of PPA for the non-surgical treatment of urinary incontinence due to urethral sphincter hypotonus.

White and Pomeroy[6] evaluated the effectiveness of an oral PPA formulation in 10 spayed female dogs with incontinence due to urethral sphincter mechanism incompetence. The dogs were all initially administered PPA at a dose of 1 mg/kg three times a day for four weeks. After this initial period, all dogs were dosed at 2 mg/kg once daily with a sustained release formulation and monitored for 1 to 3 years. The sustained release formulation contained PPA and an anti-histamine (diphenylpyraline hydrochloride). No effects of the anti-histamine were noted in the study. All signs of incontinence resolved within 24 hours of the first dose of PPA. Continence was maintained over a period ranging from one year to more than two years; however, one dog became refractory to treatment after three months. Another dog that was inadvertently treated with 2.5 mg/kg three times a day exhibited lethargy and inappetence, but the signs resolved when the dose was reduced.

In a similar study Richter and Lang[7] evaluated the effectiveness of oral PPA in 8 neutered male and 11 spayed female dogs diagnosed with primary urethral sphincter incompetence. No dog had corrective surgery and all dogs did not receive any medication for incontinence for at least two weeks prior to enrolling in the study. Some dogs had previous therapeutic attempts with diethylstilbestrol (DES) or testosterone that were not effective. All dogs with incontinence due to neurological disease and all cases with current urinary tract infections were excluded. The dogs were each administered 1.5 mg/kg PPA orally

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[1] Rigg DL, Zenoble RD, and Riedesel EA. Neoureterostomy and phenylpropanolamine therapy for incontinence due to ectopic ureter in a dog. *J. Amer. Anim. Hosp. Assoc.* 1983; 19:237 – 241.

[2] Hosgood G, Salisbury SK, Blevins WE, and Widmer WR. Unusual anatomic variation of bilateral ectopic ureters in a dog. *JAVMA.* 1989; 195:1591 – 1592.

[3] Massat BJ, et al. Cystouretropexy to correct refractory urinary incontinence due to urethral sphincter incompetence. Preliminary results in ten bitches. *Vet. Surg.* 1993; 22:260 – 268.

[4] Lane IF, Lappin MR, and Seim HB. Evaluation of results of preoperative urodynamic measurements in nine dogs with ectopic ureters. *JAVMA*. 1995; 206:1348 – 1357.

[5] Bray JP, White RAS, and Williams JM. Partial resection and omentalization: A new technique for management of prostatic retention cysts in dogs. *Vet. Surg.* 1997; 26:202 - 209.

[6] White RAS and Pomeroy CJ. Phenylpropanolamine: An alpha-adrenergic agent for the management of urinary incontinence in the bitch associated with urethral sphincter incompetence. *Vet Record.* 1989; 125: 478-480.

[7] Richter KP and Lang GV. Clinical response and urethral pressure profile changes after PPA in dogs with primary sphincter incompetence. *JAVMA.* 1985; 187: 605-611.

three times a day, except a few dogs that were given PPA twice daily due to poor owner compliance. Urinary incontinence clinically resolved in all but one male and one female dog. Following administration of PPA, the treated dogs were observed to have a significant increase in the maximum urethral pressure and maximum urethral closure pressure. Both of these values, determined by urethral pressure profiles, were decreased in all affected dogs pre-treatment when compared to control dogs. Adverse reactions included restlessness in one dog that resolved after the dose of PPA was reduced.

A masked, placebo controlled European study by Scott, Leddy, and Bernay[8] was performed with 50 female dogs presumed to have an underlying urethral sphincter mechanism incompetence. The study found 1 mg/kg of PPA administered three times a day in a 5% oral solution in sorbitol syrup effective in eliminating all unconscious urination in 85.7% of the treated dogs on day 28 of treatment. In the vehicle control group (25 of the 50 dogs), unconscious urination resolved in 33.3% of the dogs on day 28. There was a minor increase in the incidence of vomiting and diarrhea in the PPA treated dogs.

Although the frequency of administration may range from one to three times daily among the different studies and differing formulations of PPA, the reference studies support a dosage of 2 mg/kg administered twice daily.

B. Substantial Evidence:

1. Multi-Center 28-day Placebo-Controlled Clinical Field Study

   a. Study Title and Number: A Multi-center Clinical Evaluation of Phenylpropanolamine Chewable Tablets for the Control of Urinary Incontinence in Dogs due to Sphincter Hypotonus, PLI-CL001.

   b. Investigators and Locations:

Investigator Name	City	State
Toni Harris, DVM	Charlotte	NC
Jessica Fellers, DVM	Charlotte	NC
Susan Bloss, DVM	Colorado Springs	CO
Jay Emple, DVM	Atlanta	GA
Mark Epstein, DVM	Gastonia	NC
Samuel Geller, VMD	Quakertown	PA
Stephen Pittenger, DVM	Houston	TX
Erik Tysklind, DVM	Indianapolis	IN
Karen Russ, DVM	Indianapolis	IN
Kristi Lively, DVM	Knoxville	TN
Jeffrey Katuna, DVM	Natick	MA
Linda Wilson, DVM	North Palm Beach	FL
Timothy Holloway, DVM	Ocala	FL

[8] Scott L, Leddy M, and Bernay F. Evaluation of phenylpropanolamine in the treatment of urethral sphincter mechanism incompetence in the bitch. *J. Small Anim. Pract.* 2002; 43(11): 493-6.

Investigator Name	City	State
Alan Krause, DVM	Ocala	FL
Kirsten Nickisch, DVM	Pocatello	ID
Lawrence Fox, DVM	River Grove	IL
Douglas Santen, DVM	Denver	CO
Cliff Barnett, DVM	Seminole	FL
Roger Sifferman, DVM	Springfield	MO
Michael Reilly, DVM	Springville	NY
Kerry Heuter, DVM	Yonkers	NY

c. Study Design

1. Objective: The study determined the clinical effectiveness and safety of PROIN chewable tablets (phenylpropanolamine HCl) for control of urinary incontinence in dogs due to urethral sphincter hypotonus when treated for 28 days.

2. Study Animals: The study enrolled 184 client-owned dogs diagnosed with urinary incontinence due to sphincter hypotonus. One hundred forty-nine female dogs (6 intact, 143 spayed) and 35 male dogs (4 intact, 31 castrated) were enrolled. The dogs ranged in age from 1 to 17 years old, represented 50 breeds including mixed breeds, and weighed 11.7 to 130.8 pounds. A total of 100 female dogs and 27 male dogs completed the study and were evaluated for effectiveness. All 184 dogs were evaluated for safety.

3. Treatment Groups

Table 1: Treatment and control groups

Treatment group	Dose mg/kg	Number and gender of Dogs
PROIN-treated	(2 mg/kg BID)	98 female 25 male
Placebo	(0 mg/kg BID)	51 female 10 male

4. Randomization: Dogs selected for the study were randomly allocated to treatment and were enrolled in a 2 PROIN: 1 placebo ratio.

5. Masking: The investigators, technicians, and pet owners collecting data in the study were masked to group assignments. A dispenser at each site, not involved in the conduct of the study, was aware of treatment group assignments for each animal. An independent statistician created randomized tables to allocate each dog to a treatment group but was unaware of which table was distributed to an individual study site.

6. Inclusion Criteria: Clinically healthy dogs, besides urinary incontinence, based on physical examination, blood work, fecal analysis, urinalysis, and systolic blood pressure. The dogs had a diagnosis of naturally occurring urinary incontinence due to sphincter hypotonus with a minimum of four accidents per week.

7. Exclusion Criteria: Failure to meet inclusion criteria; dogs being treated with sympathomimetics, tricyclic antidepressants, or monoamine oxidase inhibitors; dogs administered halogenated gas anesthetics; dogs with concurrent disease that would interfere with evaluation; dogs with underlying urinary issues; previous phenylpropanolamine (PPA) use or diethylstilbestrol (DES) use within two weeks; dogs with behavior problems; and non-compliant owners.

8. Drug Administration: Approximately 2 mg/kg PROIN or placebo administered orally twice daily (total 4 mg/kg daily dose) for 28 days.

9. Variables Measured:
   a. Primary clinical variable: Days (-7) through day 28, the owners documented all accidental urinations. The primary indicator of effectiveness was a significant reduction in the number of urinary accidents from pre-treatment to day 28.
   b. Other clinical variables:
      Physical examinations: Examinations, including body weight and systolic blood pressures, were performed on days (-7), 0, 14, and 28.
      Clinical Pathology: Hematology and serum chemistries were performed on days (-7), 0, 14, and 28. A urinalysis was performed on days (-7), 14, and 28. A urine culture and fecal analysis were also performed on day (-7).
      Palatability: The owner noted on the client diary form if the dose was: 1) administered to the dogs without food; 2) embedded in food; 3) administered by "pilling" the dog; or 4) completely refused by the dog.

10. Statistical Methods: The primary effectiveness variable, average number of accidents per 12-hour period per week, was analyzed for female dogs only. A generalized linear mixed model with a log link was used for the repeated measures. Fixed effect terms in the model were treatment, week, and treatment by week interaction; site was a random effect.

    The body weights and clinical pathology were analyzed by repeated measures mixed model, including the treatment, sex, day, treatment-by-sex, treatment-by-day, and treatment-by-sex-by-day interaction in the model. Site and site-by-treatment interaction were included as random effects. As for the covariance structure, the most appropriate structure based on the Akaike Information Criterion (AIC) was selected among the following for each of the variables: compound symmetry, first degree autoregressive, first degree heterogeneous autoregressive. Summary statistics on body weights and number of dogs that gained or lost weight between day 0 and day 28 as well as day 0 and day 14 were also calculated. Percent change in body weights between day 0 and day 28 was summarized, and analyzed by mixed model. The mixed model had treatment and sex in the model and the site and site-by-treatment interaction as random effects. Statistical significance was evaluated at two-sided 10% significance level.

d. Results:

1. PROIN was demonstrated to be effective by a significant ($p < 0.0064$) decrease in urinary accidents per week.

Table 2: Mean urinary accidents per week by treatment group, females

Week	Mean Urinary Accidents (PROIN-treated, N=66)	Mean Urinary Accidents (Placebo, N=34)
Pretreatment	9.0	7.8
1	3.9	4.8
2	2.5	4.1
3	1.5	3.1
4	1.6	2.8

Effectiveness was not demonstrated in males either by dose group, time, or in dose group by time interaction.

Table 3: Mean urinary accidents per week by treatment group, males

Week	Mean Urinary Accidents (PROIN-treated, N=20)	Mean Urinary Accidents (Placebo, N=7)
Pretreatment	8.8	8.1
1	5.0	4.6
2	3.8	4.1
3	4.0	3.6
4	3.7	4.6

2. Other Variables:

Weight: Nineteen (16.1%) of the PROIN-treated dogs lost ≥5% body weight by day 28, as compared to four (6.8%) of the placebo dogs. Three (2.5%) of the PROIN-treated dogs lost ≥10% body weight compared to zero (0%) of the placebo dogs.

Table 4: Percent Body Weight Loss from day 0 to the last exam[1]

Group	5.0-9.9%	≥10.0%	Total
PROIN-treated (N=118)	13.5%	2.5%	16.1%
Placebo (N= 59)	6.8%	0.0%	6.8%

[1] The "N" for weight loss is PROIN-treated N=118 and placebo N=59 because seven dogs did not have a final weight at the time of withdrawal from the study.

Systolic blood pressure: Nineteen (15.4%) PROIN-treated dogs demonstrated clinical hypertension (≥ 160 mm Hg) at one time point during the study on either day 14 or day 28. Five (4.1%) PROIN-treated dogs demonstrated a sustained hypertension (≥160 mm Hg on day 14 and 28). A total of twenty-four (19.5%) PROIN-treated dogs demonstrated clinical or sustained hypertension.

Seven (11.4%) placebo dogs demonstrated clinical hypertension and two (3.2%) demonstrated sustained hypertension. A total of nine (14.7%) placebo dogs demonstrated clinical or sustained hypertension.

Palatability: The owners offered PROIN twice daily for 14-28 days to their dogs. The PROIN-treated dogs voluntarily consumed 53.9% of the doses without food and 33.7% of the doses with food. Owners pilled 12.1% of the doses. Dogs did not accept 0.3% of the doses.

Table 5: Acceptance of doses by category

Acceptance	PROIN-treated (# of doses) N= 6144	Placebo (# of doses) N= 2854
Without food	53.9%	82.7%
With food	33.7%	11.9%
Pilled	12.1%	5.2%
Not accepted	0.3%	0.2%

Clinical Pathology: There were no clinically significant drug-related findings in hematology or serum chemistries during the study.

Sixteen (13%) PROIN-treated dogs had proteinuria versus five (8%) placebo dogs.

e. Adverse Reactions: There were two deaths during the study. A PROIN-treated dog developed a cranial abdominal mass effect, vomiting, and lethargy with an unknown relation to treatment. The dog was euthanized and necropsy declined. A placebo dog developed liver insufficiency and was euthanized. Necropsy revealed hepatitis unrelated to treatment. Two PROIN-treated dogs demonstrated multiple adverse reactions suspected to be drug-related. One dog displayed disorientation, nervous behavior, anorexia, 7.7% body weight loss, and hypertension with proteinuria. Another dog showed restless behavior, panting, lethargy, 2.8% body weight loss, and proteinuria.

Table 6 below shows the most commonly reported adverse reactions. All other adverse findings were considered to be unrelated to treatment.

Table 6: Adverse reactions in the 28-day placebo-controlled clinical study

Adverse Reactions	PROIN-treated (N=123)	Placebo (N=61)
Emesis	20.3%	8.2%
Hypertension (≥ 160 mm Hg)[1]	19.5%	14.7%
Anorexia	16.3%	3.3%
Body weight loss (≥5%)[2]	16.1%	6.8%
Proteinuria	13.0%	8.2%
Anxiety/aggression/behavior change	9.7%	3.2%
Diarrhea	7.3%	9.8%
Polydipsia	6.5%	9.8%
Lethargy	5.7%	1.6%
Musculoskeletal disorder	3.2%	1.6%
Insomnia/sleep disorder	2.5%	0.0%

[1] one or more systolic blood pressure readings ≥160 mm Hg
[2] The "N" for weight loss is PROIN-treated N=118 and placebo N=59 because seven dogs did not have a final weight at the time of withdrawal from the study.

f. Conclusion: PROIN administered at 2 mg/kg orally twice a day was effective for the control of urinary incontinence based on a decrease in urinary accidents per week as compared to placebo. Treatment with PROIN was associated with an increased incidence of emesis, hypertension, anorexia, weight loss, proteinuria, and behavioral changes.

2. Multi-Center, Open-Label, Clinical Field Study

a. Study Title and Number: Clinical Evaluation of the Long Term Effectiveness and Safety of Phenylpropanolamine Chewable Tablets for the Control of Urinary Incontinence in Dogs, PLI-CL002

b. Investigators and Locations:

Investigator Name	City	State
Toni Harris, DVM	Charlotte	NC
Jessica Fellers, DVM	Charlotte	NC
Susan Bloss, DVM	Colorado Springs	CO
Jay Emple, DVM	Atlanta	GA
Mark Epstein, DVM	Gastonia	NC
Samuel Geller, VMD	Quakertown	PA
Stephen Pittenger, DVM	Houston	TX
Erik Tysklind, DVM	Indianapolis	IN
Karen Russ, DVM	Indianapolis	IN
Kristi Lively, DVM	Knoxville	TN
Jeffery Katuna, DVM	Natick	MA
Linda Wilson, DVM	North Palm Beach	FL
Timothy Holloway, DVM	Ocala	FL
Alan Krause, DVM	Ocala	FL
Kirsten Nickisch, DVM	Pocatello	ID
Lawrence Fox, DVM	River Grove	IL

Investigator Name	City	State
Douglas Santen, DVM	Denver	CO
Roger Sifferman, DVM	Springfield	MO
Michael Reilly, DVM	Springville	NY
Kerry Heuter, DVM	Yonkers	NY
Cliff Barnett, DVM	Seminole	FL

c. Study Design:

1. Objective: The study determined the long-term clinical effectiveness and safety of PROIN chewable tablets (phenylpropanolamine HCl) for control of urinary incontinence in dogs due to urethral sphincter hypotonus when treated for up to six months.

2. Study Animals: The study was a continuation for 157 client-owned animals from the 28-day placebo-controlled clinical study with a diagnosis of primary incontinence due to sphincter hypotonus (PLI-CL001). The study enrolled approximately 128 females (4 intact, 124 spayed) and 29 males (3 intact, 26 castrated), representing 47 breeds. At the time of the study report, a total of 125 dogs completed the study to day 90 and 104 dogs completed the study to day 180.

3. Treatment Groups: During the 6-month open-label clinical study, all dogs (128 females, 29 males) received PROIN (phenylpropanolamine HCl) at 2 mg/kg body weight twice a day.

4. Inclusion Criteria: Each animal completed the 28-day placebo-controlled study (PLI-CL001) to at least the day 14 evaluation prior to enrollment.

5. Exclusion Criteria: No change from PLI-CL001

6. Drug Administration: Approximately 2 mg/kg PROIN administered orally twice daily (4 mg/kg total daily dose) for 6 months.

7. Variables Measured:
   a. Primary clinical variable: The investigator recorded client effectiveness evaluations at 30 day intervals. Client satisfaction was the primary endpoint.

   b. Other clinical variables
      Client Diary: The owner recorded problems with dosing, missed doses, urinary accidents, and possible adverse events days 0-180.
      Physical examinations: An examination, including body weight and systolic blood pressure, was performed on days 90 and 180.
      Clinical Pathology: Hematology, serum chemistry, and urinalysis were performed on days 90 and 180.

8. Statistical Methods: Body weights and clinical pathology were analyzed by pairwise comparisons of the treatment days (day 0 and day 90, day 0 and day 180, day 90 and day 180). Sex effect was in the model

along with the day effect. Site and site-by-treatment interaction were included as random effects. Summary statistics on body weights and number of dogs that gained or lost weight between day 0 and day 180 as well as day 0 and day 90 were also calculated. Percent change in body weights between day 0 and day 90 was summarized, and analyzed by one-sample t-test. Statistical significance was evaluated at two-sided 10% significance level.

d. Results:

1. Client Satisfaction survey: At one month, 91.3% of the owners reported urinary continence was restored to their satisfaction. By day 180, client satisfaction rose to 98.1%.

2. Other Variables:
Client Diary: During the first month, there was an average of three accidents per dog. During the second month, the number of reported accidents decreased to less than two accidents per dog. In the third month, the number of accidents fell to just over one accident per dog.

Weight: Thirty-one of 125 (24.8%) dogs demonstrated a body weight loss of ≥ 5%. The following table shows the percent of dogs with weight loss upon initiation of PROIN treatment to the final examination.

Table 7: Percent body weight loss from initiation of PROIN to final clinical exam

Day	5.0-9.9%	10.0-20.0%	>20.0%	Total
Day 90 (N= 125)	5.6%	0.0%	0.0%	5.6%
Day 180 (N= 104)	16.3%	4.8%	1.9%	23.0%
Total (N= 125)	19.2%	4.0%	1.6%	24.8%

Of the nineteen (16.1%) PROIN-treated dogs from the 28-day placebo-controlled clinical study that lost ≥ 5% body weight, ten (52.6%) dogs regained some or all of the weight lost, two (10.5%) dogs lost additional weight, and one (5.2%) dog remained the same weight. Six (31.5%) dogs were not enrolled in the study.

Twenty-five (20.0%) of 125 dogs gained weight during the 6-month open label clinical study.

Systolic blood pressure: Of the dogs entering the 28-day study, 55 dogs (30.2%) had a blood pressure reading of ≥160 mm Hg on day (-7) and 60 dogs (33.3%) had a blood pressure reading of ≥160 mm Hg on day 0. On day 90, 32 dogs (25.9%) were hypertensive (≥160 mm Hg). On day 180, 30 dogs (28.5%) were hypertensive (≥160 mm Hg). Because some dogs were hypertensive on both day 90 and 180, an overall incidence of hypertension was calculated by the number of

individual dogs. The overall incidence of hypertension was 43 dogs (34.6%).

Palatability: Owners did not experience difficulty dosing >95% of the administered doses.

Clinical Pathology: There were no clinically significant drug-related findings in hematology or serum chemistries during the study.

The overall incidence of proteinuria during the 6-month open-label clinical study was 15.3%.

e. Adverse Reactions: Table 8 below lists the most common adverse reactions during the 6-month open-label clinical study. All other adverse findings were considered to be unrelated to treatment.

Table 8: Adverse reactions in the 6-month open label clinical study

Adverse Events	Total N=125
Hypertension (≥160 mm Hg)[1]	34.6%
Body weight loss (≥5%)	24.8%
Emesis	19.7%
Proteinuria	15.3%
Anorexia	10.2%
Diarrhea	6.4%
Lethargy	5.7%
Anxiety/behavior change/aggression	5.7%

[1] Percent of dogs with systolic blood pressures of ≥160 mm Hg on day (-7) were 30.2% and on day 0 were 33.3%.

There were seven severe adverse events, one that was suspected to be treatment related, one with an unknown relation to treatment, and five unrelated to treatment. One dog, with an adverse reaction suspected to be related to treatment, demonstrated progressively worsening hypertension in conjunction with proteinuria. One dog, with preexisting heart disease and an adverse event with an unknown relation to treatment, developed systolic failure, S3 gallop, hypertension, left ventricular hypertrophy, and showed an increase in the grade of the heart murmur by day 171.

f. Conclusions: PROIN administered orally at 2 mg/kg twice daily was effective for the control of urinary incontinence for 180 days based on 98.1% owner satisfaction. Treatment with PROIN was associated with an increased incidence of weight loss, hypertension, emesis, proteinuria, and anorexia.

III. TARGET ANIMAL SAFETY:

A. Margin of Safety Study

1. Phenylpropanolamine (PPA) Target Animal Safety Study in Dogs (Study No. 202-0674d)

   a. Type of Study: Laboratory, under Good Laboratory Practices

   b. Investigator: John W. Byrd, PhD
   Las Cruces, NM

   c. General Design:

      1. Purpose: To evaluate the safety of phenylpropanolamine (PPA) in dogs given twice daily doses at 1X, 3X, or 5X the recommended dose (2 mg/kg) for 182 days.

      2. Test Animals: Thirty-two Beagle dogs (16M, 16F), ranging in weight from 15 - 35 lbs. and 1 – 6 years of age, were randomly assigned to 4 treatment groups of 8 dogs (4M, 4F) each.

      3. Control: Control dogs received placebo tablets identical to active tablets in size, shape, and appearance.

      4. Dose Form: Scored tablets containing 0, 25, or 50 mg PPA.

      5. Route of Administration: Oral.

      6. Dosage: Table 9 lists the treatment groups and the dosages:

      Table 9: Treatment Groups and Dosages

Group Number	Treatment	Dose Level (mg/kg) twice daily	Duration (days)	Number of Animals
1	0X	0	182	4M + 4F
2	1X	2	182	4M + 4F
3	3X	6	182	4M + 4F
4	5X	10	182	4M + 4F

      7. Duration of Treatment: 182 days

      8. Variables Measured: Following baseline measurements, physical examinations (including blood pressure and electrocardiography performed within 4 hours of dosing), body weights, hematology, blood chemistry, urinalysis, and fecal evaluations were performed every two

weeks during the treatment period. General and post-dose observations were made twice daily, and food and water consumption were measured daily during treatment. Ophthalmic evaluations were performed before, in the middle, and at the end of the treatment period. Gross necropsy and histopathology were conducted at the conclusion of the study.

9. Statistical Methods: Continuous variables measured at necropsy were analyzed using analysis of variance (ANOVA) with treatment and sex and their interaction as factors in the ANOVA model. Continuous variables measured repeatedly were analyzed using repeated measures ANOVA with the average of baseline values as a covariate. Treatment, sex, time and all their interactions were included as factors in the repeated measures ANOVA. The significance level was set to 0.10 for evaluation of treatment and treatment by time interactions and to 0.05 for evaluation of sex and treatment by sex interactions. Fisher's Exact test was used to test treatment effect within day and sex for the categorical variables.

d. Results:

1. Daily Observations: Animals were observed twice daily and for 1 hour following morning and afternoon drug administration. Vomiting and loose stool occurred in a dose-related fashion, with the 5X dogs having the highest incidence of both (less than 4% of the observations). Most of the vomiting episodes took place within 1 hour of dosing. Dogs administered PPA exhibited anxious/restless behavior more frequently than the control group; total incidences out of 2,912 observations (per group) for the 0X, 1X, 3X, and 5X groups were 0.5%, 7.0%, 1.6%, and 3.2%. One dog was responsible for 94% of the anxious/restless observations in the 1X group, and one dog in the 3X group had 60% of the observations.

2. Physical Examinations: One dog in each of the 1X and 3X groups developed gallop heart sounds that were noted after treatment began in 12 of 13 and 6 of 13 physical exams, respectively. Other physical exam findings were incidental and not related to the test article.

3. Blood Pressure: Systolic, diastolic, and mean arterial pressures (MAP= [(2x diastolic in mm Hg) + systolic in mm Hg] ÷ 3) were used to evaluate blood pressure differences between groups. Systolic blood pressure was statistically significantly higher in all three PPA-dosed groups compared to the control group. Systolic means were within the normal reference range.

Table 10: Mean Systolic Blood Pressure Values During Treatment

Variable	Group	Mean (mm Hg)[1]	p-value
Systolic Blood Pressure	0X	156.18	
	1X	167.46	0.0005
	3X	170.88	<0.0001
	5X	169.19	<0.0001

[1]Normal systolic blood pressure ≤ 180 mm Hg

Diastolic and MAP were statistically significantly higher in the 3X and 5X groups, and in the 1X males, compared to the control group; some of the mean values were in the hypertensive range.

Table 11: Mean Diastolic and Mean MAP Values During Treatment

		Male Dogs		Female Dogs	
Variable	Group	Mean[1] (mm Hg)	p-value	Mean[1] (mm Hg)	p-value
Diastolic Pressure	0X	93.76		94.75	
	1X	110.32*	<0.0001	91.95	0.4634
	3X	107.72*	0.0003	114.83*	<0.0001
	5X	111.05*	<0.0001	106.99*	0.0014
Mean Arterial Pressure	0X	118.59		115.30	
	1X	132.21*	0.0005	118.10	0.4538
	3X	127.59*	0.0149	136.08*	<0.0001
	5X	131.92*	0.0004	132.10*	<0.0001

[1]Normal diastolic blood pressure ≤ 100 mm Hg; Normal MAP < 127 mm Hg
*Indicates values in the hypertensive range

When the individual dog averages (13 exams) for systolic, diastolic, and mean arterial pressure were evaluated instead of group averages, the difference between the control group and the 1X group was minimal. The more pronounced differences were between the two higher dose groups (3X and 5X) and the control group. There were more dogs whose individual average diastolic and MAP values were above the normal range, and more individual readings above the normal range, in the 3X and 5X groups.

Table 12: High Individual Blood Pressure Values

Variable	Group	#of dogs whose individual average is above range[1,2,3]	Highest individual value (mm Hg)	Total # of individual readings[4] above range
Systolic Blood Pressure	0X	1/8	214	19
	1X	1/8	217	20
	3X	1/8	205	36
	5X	2/8	211	33
Diastolic Blood Pressure	0X	3/8	146	45
	1X	4/8	148	56
	3X	8/8	142	83
	5X	7/8	157	79
Mean Arterial Pressure	0X	3/8	170	36
	1X	2/8	165	37
	3X	7/8	172	78
	5X	4/8	183	66

[1]Normal systolic blood pressure ≤ 180 mm Hg
[2]Normal diastolic blood pressure ≤ 100 mm Hg
[3]Normal mean arterial pressure < 127 mm Hg
[4]Thirteen exams x 8 dogs/group = 104 total readings per group

4. Heart Rate: Electrocardiograms were performed 13 times over the 182-day treatment period, for a total of 104 exams per 8-animal group. Heart rates taken from electrocardiograms, averaged over study days, were statistically significantly lower in the 3X (p=0.0187) and 5X (p=0.0392) groups compared to the control group. Mean heart rates for the four groups were within the normal reference range of 70-120 beats per minute on all physical exam days, but heart rates below the normal range were observed in 5, 35, 46, and 42 of the 104 exams for each of the 0, 1, 3, and 5X groups, respectively. There was one dog in each of the 1X and 5X groups that had an elevated heart rate between 150-180 beats per minute on at least 2 of the 13 physical exam days.

Table 13: Mean Heart Rates and Values Below Normal

Group	Mean[1] (beats/min)	p-value	# of values below normal[2]	Lowest Value (beats/min)
0X	95.03	N/A	5	69
1X	89.45	0.4008	35	51
3X	78.65	0.0187	46	60
5X	80.87	0.0392	42	51

[1]Normal reference range: 70-120 beats per minute from Merck Veterinary Manual
[2] Thirteen exams x 8 dogs/group = 104 total readings

5. Body Weight: Average male group body weights for the 0, 1X, 3X, and 5X groups increased 1, 3, 2, and 3 lbs., respectively, over the 182-day dosing period. However, average female group weights decreased 3, 3, 2, and 5 lbs., respectively, indicating that females in all four groups,

including the control group, lost weight over the course of the study. A decline in body scores assigned during physical exams also accompanied the loss of body weight in female dogs in all four study groups. Weight loss was substantial in some individual female dogs. Maximum weight loss in individual female dogs in the 0X, 1X, 3X, and 5X groups was 23%, 33%, 13%, and 25% of total body weight, respectively. Dogs in all 4 groups had lower food consumption averages during the first week after initiation of treatment, with 2 individual dogs in the 5X group eating less than 50% of their pretreatment food averages.

6. Hematology and Blood Chemistry: Platelet counts were statistically significantly higher ($p<0.10$) in at least one of the PPA-dosed groups compared to the control group on 12 of 13 exams, with individual values up to 1.4 times the upper limit of normal (ULN) in the 3X and 5X groups.

   Serum alanine aminotransferase (ALT), averaged over study days, was significantly higher in the 3X ($p=0.0474$) and 5X ($p=0.0117$) groups compared to the control group. There were more dogs and more values above the normal ALT range in the 3 PPA-dosed groups compared to the control, but increased values were transient and less than 1.8 times ULN. All dogs had ALT values in the normal range at the conclusion of the study.

   Individual dogs in the 1X, 3X, and 5X groups had increases in serum lactate dehydrogenase (LDH) above the normal reference range (especially the 5X group) whereas none of the control dogs did. These increased LDH values were also transient, and all dogs had normal values at the end of the study.

7. Other Variables: There were no clinical findings attributable to PPA on the ophthalmic exams, electrocardiogram evaluations, urinalysis, fecal analysis, or gross necropsy and histopathology.

e. Conclusions: This study demonstrated the safety of phenylpropanolamine administered to dogs at 2, 6, and 10 mg/kg twice daily for 6 months. The most pronounced effects were a dose-dependent increase in blood pressure and a dose-dependent decrease in heart rate. There were no findings in ophthalmic examinations or histologic evaluation of tissues collected at necropsy indicative of target organ damage caused by chronic hypertension. A decline in body weight and condition was noted in females in all groups. Temporary elevations of platelet count and serum ALT were observed in dogs administered PPA.

B. Acute Tolerance Study

1. Acute Tolerance Study in Dogs Receiving Oral Phenylpropanolamine (PPA) (Study No. 202-0673d)

   a. Type of Study: Laboratory, under Good Laboratory Practices

   b. Investigator: John W. Byrd, Ph.D.
   Las Cruces, NM

   c. General Design:

      1. Purpose: To evaluate the safety of phenylpropanolamine (PPA) in dogs given twice daily doses at 10X the recommended dose (2 mg/kg) for 21 consecutive days.

      2. Test Animals: Twelve adult female Beagle dogs, ranging in weight from 14-23 lbs. and 1-2 years of age were randomly assigned to 2 treatment groups of 6 dogs each.

      3. Control: Control dogs received placebo tablets identical to active tablets in size, shape, and appearance.

      4. Dose Form: Scored tablet containing 0, 25, or 50 mg PPA.

      5. Route of Administration: Oral

      6. Dosage: Table 14 lists the groups and dosages:

      Table 14: Treatment Groups and Dosages

Group Number	Treatment	Dose Level (mg/kg) twice daily	Duration (days)	Number of Animals
1	0X	0	21	6F
2	10X	20	21	6F

      7. Duration of Dosing: 21 days

      8. Variables Measured: Following baseline measurements, physical examinations (including blood pressure and electrocardiography performed within 4 hours of dosing), body weights, hematology, blood chemistry, urinalysis, and fecal evaluations were performed on study days 7, 14, and 21. General and post-dose observations were made twice daily, and food and water consumption were measured daily during treatment. Ophthalmic evaluations were performed before, and at the end of the treatment period. Gross necropsy and histopathology were conducted at the conclusion of the study.

      9. Statistical Methods: Continuous variables measured repeatedly were analyzed using repeated measures ANOVA with the average of

baseline values as a covariate. Treatment, time, and their interaction were included as factors in the repeated measures ANOVA. The significance level was set to 0.10 for evaluation of treatment and treatment by time interaction. Fisher's Exact test was used to test treatment effect within day for the categorical variables.

d. Results:

1. Daily Observations: Animals were observed twice daily, and for 1 hour following morning and afternoon drug administration. All 6 dogs in the 10X group vomited at least once during the 21-day treatment period (less than 5% of the observations), whereas only 1 of the control dogs vomited. Most of the vomiting episodes took place within 1 hour of dosing.

2. Blood Pressure: Systolic, diastolic, and mean arterial pressures (MAP) were used to evaluate blood pressure differences between groups. Systolic pressure was statistically significantly higher ($p=0.0777$) in the 10X group compared to the control group, but mean values were within normal range for both groups. Diastolic means were above the normal range in the 10X group on days 7 and 21, and in the control group on day 14. The 10X dogs had hypertensive mean MAP values on days 7 and 21, whereas the MAP means for the control dogs were in the normal range. Individual 10X dogs had higher systolic, diastolic, and MAP readings than control dogs on days 7, 14, and 21.

Table 15: Mean Systolic Blood Pressure Values During Treatment

Variable	Group	Mean* (mm Hg)	Highest Individual Value (mm Hg)	p-value
Systolic Blood Pressure	0X	148.62	186	
	10X	168.91	205	0.0777

*Normal systolic blood pressure range ≤ 180 mm Hg

3. Heart Rate: Heart rates were calculated from the electrocardiograms. There was a trend in 10X dogs for lower heart rates following initiation of PPA dosing. Four of 6 dogs in the 10X group had heart rates below the normal reference range on day 7, whereas none of the control dogs did. One 10X dog had readings below normal on all 3 exam days after dosing began.

4. Hematology and Blood Chemistry: Hematocrit (HCT), hemoglobin (HGB), and red blood cell (RBC) counts were statistically significantly higher ($p<0.10$) in the 10X dogs on study days 7 and 14 compared to the control dogs, with means for HCT and RBC variables in the 10X dogs above the normal reference range on day 7. These findings were consistent with transient dehydration in the 10X dogs that occurred shortly after initiation of dosing with PPA.

White blood cell (WBC) counts were statistically significantly higher ($p=0.0013$) in the 10X group on study day 21, with 2 dogs having individual values up to 1.3 times the upper limit of normal (ULN).

The 10X group had statistically significantly higher ($p<0.0001$) platelet counts overall compared to the control group. The 10X group mean values were numerically higher than the control group on all 3 exam days, and were above the normal reference range on days 7 and 14. The highest mean platelet value was on day 7, with individual values up to 1.5 times ULN.

Serum ALT was statistically significantly higher ($p=0.0496$) in the 10X dogs on day 7. Mean ALT values for both groups were within the normal reference range on all 3 exam days, but 2 dogs in the 10X group had values up to 1.4 times ULN on day 7. These individual increases were transient, and all 10X dogs had ALT values in the normal range on days 14 and 21.

5. Urinalysis and Water Consumption: Urine specific gravity and water consumption were statistically significantly higher overall ($p=0.0176$, $p=0.0204$, respectively) in the 10X dogs compared to the control dogs. Higher urine specific gravity was likely due to transient dehydration, as was the compensatory water intake.

6. Other Variables: There were no clinical findings attributable to PPA on the physical exams, ophthalmic exams, electrocardiogram evaluation, fecal analysis, or gross necropsy and histopathology.

e. Conclusions: This study demonstrated the effects of phenylpropanolamine administered to dogs at 20 mg/kg twice daily for 21 days. The most significant effect was an increase in systolic blood pressure. There were no changes found in ophthalmic examinations or histologic evaluation of tissues collected at necropsy indicative of target organ damage caused by chronic hypertension. There was a trend towards lower heart rates in the 10X dogs. Transient, subclinical dehydration occurred in 10X dogs, along with temporary elevations of RBC, WBC, platelet count, and serum ALT.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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 NADA.

V. USER SAFETY:

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

Not for human use.

Keep out of reach of children.

Consult a physician in case of accidental ingestion by humans.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that PROIN Chewable Tablets, when used according to the label, is safe and effective for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

A. Marketing Status:

The drug is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to diagnose urinary incontinence and to determine that the dog's condition is not due to other medical or surgical reasons.

B. Exclusivity:

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.