Date of Approval: March 29, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-517

PROIN ER™

phenylpropanolamine hydrochloride extended-release tablets

Dogs

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

Sponsored by:

Pegasus Laboratories, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-517

B. Sponsor

Pegasus Laboratories, Inc.,
8809 Ely Rd.,
Pensacola, FL 32514

Drug Labeler Code: 055246

C. Proprietary Name

PROIN ER™

D. Drug Product Established Name

Phenylpropanolamine hydrochloride extended-release tablets

E. Pharmacological Category

Sympathomimetic amine

F. Dosage Form

Tablets

G. Amount of Active Ingredient

18, 38, 74, or 145 mg of phenylpropanolamine hydrochloride per tablet

H. How Supplied

Packaged in bottles containing 30 or 90 tablets

I. Dispensing Status

Rx

J. Dosage Regimen

The recommended dosage is 2 to 4 mg/kg (0.9 to 1.8 mg/lb) of body weight once daily according to Table I.1 below. Administer PROIN ER™ with food. Do not split or crush tablets.

Dogs weighing less than 10 pounds cannot be safely dosed because tablet administration would result in a dose over 4 mg/kg.

Table I.1 Dose Administration[a]

Body weight in pounds	PROIN ER™
10-20	18 mg
21-40	38 mg
41-80	74 mg
81-125 [b]	145 mg

[a] Body weight should be rounded to the nearest pound.
[b] Dogs exceeding 125 lbs should receive the appropriate combination of tablets to achieve the recommended dosage.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

PROIN ER™ is indicated for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

II. EFFECTIVENESS

A. Dosage Characterization

The dosage for PROIN ER™ (phenylpropanolamine hydrochloride extended-release tablets) is based on the dosage regimen of PROIN® Chewable Tablets and does not exceed a maximum daily dose of 4 mg/kg. The dosage characterization for PROIN® Chewable Tablets (phenylpropanolamine hydrochloride) is described in the Freedom of Information (FOI) Summary (NADA 141- 324), dated August 4, 2011. The FOI Summary for PROIN® Chewable Tablets describes findings from eight scientific publications of phenylpropanolamine (PPA) dose-response studies in dogs. As described in these studies, the frequency of administration ranges from one to three times daily for the different formulations of PPA. The referenced studies support a dosage of 2 mg/kg for PROIN® Chewable Tablets administered twice daily (a total daily dose of 4 mg/kg). The tablet strengths of PROIN ER™ are assigned to specific weight ranges of dogs, to achieve a maximum daily dose of no greater than 4 mg/kg, consistent with the maximum daily dose of PROIN® Chewable Tablets. PROIN ER™, when administered

according to label directions for the assigned dog weight, provide a total daily dose range of 2 - 4 mg/kg once a day.

B. Substantial Evidence

The effectiveness of PROIN ER™ was demonstrated in the clinical field study described below. One hundred and nineteen client-owned dogs were enrolled. The study enrolled dogs previously diagnosed with urinary incontinence (UI) due to Urethral Sphincter Mechanism Incompetence (USMI) who were administered PROIN® Chewable Tablets and considered controlled for their incontinence.

For one week, between Day -7 and Day -1, the owners recorded the number of accidents per day and whether the dog received the PROIN® Chewable Tablet doses. Dogs were then transitioned to once a day dosing of PROIN ER™. For the first 28 days of PROIN ER™ administration, the owner recorded how many urinary accidents occurred each day. The ratio of average daily incidence of UI during the baseline period between Day -7 to Day -1 of administration of PROIN® Chewable Tablets was compared to the response measurement period between Day 21 to Day 27 of administration of PROIN ER™. Seventy five of the 104 dogs who completed the study had zero accidents between Day -7 to Day -1 and maintained zero accidents between Day 21 to Day 27. See Tables II.2 and II.3 below for complete results.

Title: A Multi-Center Clinical Study of the Effectiveness, Safety, and Oral Acceptability of PROIN™ (Phenylpropanolamine HCl) Extended Release Tablets for the Control of Urinary Sphincter Mechanism Incontinence in Dogs; Study Number PLI-CL016

Study Dates: September 25, 2015 - September 9, 2016

Study Locations:

Battle Creek, Michigan
Bradenton, Florida
Dallas, Texas
Fort Collins, Colorado
Lawrence, Kansas
Quakertown, Pennsylvania
Rochester, New York
Springfield, Missouri
Wellington, Colorado

Study Design: This was a multicenter, prospective, open-label clinical field study. The study was conducted in accordance with Good Clinical Practices.

Objective: To evaluate the effectiveness, safety, and oral acceptability of an extended release tablet formulation of phenylpropanolamine (PPA).

Study Animals: The study enrolled 119 client-owned dogs diagnosed with urinary incontinence (UI) due to Urethral Sphincter Mechanism Incompetence (USMI) controlled with administration of PROIN® Chewable Tablets. There were 113 spayed females and 6 neutered males. There were 79 (66.4%) purebred dogs and 40 (33.6%) mixed breed dogs. The most common purebred dogs were the Labrador Retriever with 14 (11.8%) dogs, the Doberman Pinscher with 11 (9.2%) dogs, and the German Shepherd with 8 (6.7%) dogs. Dogs ranged in age from 1 - 16 years and weighed 4.9 - 81.8 kg at the time of screening. During the field study, dogs were administered routine vaccinations and common concurrent medications included heartworm preventatives, antiparasiticides, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs). A total of 104 dogs completed the study and were evaluated for effectiveness. All 119 dogs were evaluated for safety.

Experimental Design:

Treatment Groups: All enrolled dogs were transitioned from PROIN® Chewable Tablets to PROIN ER™.

Inclusion criteria: Diagnosed with naturally occurring UI due to USMI; did not have other conditions causing UI such as anatomical defects of the bladder/urethra/ureters, submissive micturition, surgeries causative to UI, neurological disease causative to UI, recurrent urinary tract infections, polyuria/polydipsia (PU/PD), or concurrent disease associated with PU/PD such as diabetes or renal disease; did not receive medications that could affect UI; did not have significant health abnormalities; average systolic blood pressure (BP) ≤160 mmHg at screening; received PROIN® Chewable Tablets for ≥30 days preceding the screening visit and through the 7 day baseline study period; owner assessment at screening visit and on Day 0 indicated the UI was adequately controlled with PROIN® Chewable Tablets; no scheduled surgery during the study; no administration of estrogen supplementation, systemic corticosteroids, sympathomimetic drugs, tricyclic antidepressants, halogenated gas anesthetics, monoamine oxidase inhibitors, or treatments known to affect urinary output such as diuretics or fluid therapy for 6 weeks prior and during study.

Exclusion criteria: Failure to meet the inclusion criteria.

Drug Administration: The owner administered the dose at home. The dose was based on body weight according to the dosing table for a target dose of 2 - 4 mg/kg and administered orally once a day in the morning with or without food for 180 days.

Table II.1. Dose Administration[a]

Body weight in pounds	Body weight in kilograms	PROIN ER™ Tablet strength
10 - 20	4.5 - 9.1	18 mg
21 - 40	9.5 - 18.2	38 mg
41 - 80	18.6 - 36.4	74 mg
81 - 125	36.8 - 56.8	145 mg
>125	>56.8	Combination[b]

[a] Body weight was rounded to the nearest pound (for example, 20.4 lbs. was rounded to 20 lbs., and 20.5 lbs. was rounded to 21 lbs.).
[b] Dogs exceeding 125 lbs. received the appropriate combination of tablets to yield a dose of 2 - 4 mg/kg.

Measurements and Observations: Baseline physical examination (including heart rate, respiratory rate, body weight, body temperature, and blood pressure), hematology, serum chemistry, and urinalysis assessments were performed prior to administration of the first PROIN ER™ dose (Day 0), and at study visits on Day 28 and Day 180. Physical examination including blood pressure was also performed during study visits on Day 21, Day 60, and Day 120.

During the Day -7 to Day -1 baseline period, dogs were administered PROIN® Chewable Tablets (prior to transition to administration of PROIN ER™), and owners recorded the number of accidents per day and whether the dog received the PROIN® Chewable Tablet dose according to routine dosing regimen. At the end of the baseline period, owners recorded whether the dog's UI was well controlled with PROIN® Chewable Tablets.

Dogs were then transitioned to once a day dosing of PROIN ER™. For the first 28 days of administration, owners recorded the following each day:

- time of treatment;
- number of tablets administered;
- whether the treatment was administered within 4 hours of a meal;
- how the treatment was accepted based on a scale 1 - 4:
    1) Tablet voluntarily consumed,
    2) Tablet voluntarily consumed in a small amount of food,
    3) Tablet given by opening the dog's mouth, placing tablets at the back of the mouth, and gently holding the mouth closed until the dog swallows,
    4) Tablets not consumed or refused;
- if there were any treatment issues or health abnormalities; and
- how many urinary accidents occurred.

At Day 28 the owner was interviewed to obtain an assessment of whether the dog's UI over the 7 days preceding the clinic visit had improved, stayed the same, or worsened compared to the baseline period.

Statistical Methods: The analysis of the effectiveness variable was based on the ratio of average daily incidence of UI during the baseline period of Day -7 to Day -1 of administration of PROIN® Chewable Tablets when compared to the response measurement period Day 21 to Day 27 of administration of PROIN ER™. The ratio was calculated for each dog. However, because of the distribution of the ratios, conventional non-inferiority analysis was not applicable and therefore the data were clinically evaluated based on summary statistics.

Results: Effectiveness: Effectiveness was evaluated in 104 dogs. The primary outcome variable was the ratio of average daily incidence of UI during Day 21 through Day 27 clinic visit compared to the baseline period during Day -7 through Day -1 for each dog. There were 75 (72.1%) dogs with a ratio of 1, indicating no difference between baseline and the response measurement period. There were 19 (18.3%) dogs with a ratio of greater than 1, indicating the response measurement period was better than the baseline period. There were 10 dogs (9.6%) dogs with a ratio of less than 1, indicating the response measurement period was worse than the baseline period. Table II.2 presents the clinical effectiveness results.

Table II.2 Clinical Effectiveness Results for PROIN ER™

Ratio	Number of Dogs N=104
Ratio >1, indicating response measurement period was better than baseline period	19 (18.3%)
Ratio of 1, indicating no difference between response measurement period and baseline period	75 (72.1%)
Ratio <1, indicating response measurement period was worse than baseline period	10 (9.6%)

The mean (±std dev) average daily incidence of UI during the baseline period (PROIN® Chewable Tablets) was 0.21 (±0.17). The mean (±std dev) average daily incidence of UI during the response measurement period (PROIN ER™) was 0.18 (±0.14).

Table II.3 describes all 104 dogs by the incidence of UI during study Days -7 to -1 while receiving PROIN® Chewable Tablets compared to the incidence of UI after transitioning to PROIN ER™ during Days 21 to 27.

Table II.3. Incidence of UI when comparing PROIN® Chewable Tablet administration from Day -7 to Day -1 to PROIN ER™ from Day 21 to Day 27 for 104 dogs

PROIN® Chewable Tablets[a]	**PROIN ER™[a]**			
	0 UI	**1-2 UI**	**2-3 UI**	**3+ UI**
0 UI	75 dogs	6 dogs	1 dog	0 dogs
1-2 UI	7 dogs	0 dogs	1 dog	1 dog
2-3 UI	2 dogs	5 dogs	0 dogs	0 dogs
3+ UI	3 dogs	2 dogs	0 dogs	1 dog

[a] The UI incidence counts were categorized as 0, ≥1 and <2, ≥2 and <3, and ≥3 incidents per day.

Based on these descriptive statistics and the results summarized in the frequency cross-tabulation of incidence table (Table II.3 above), the level of control (incidence rate of UI) did not differ when animals were transitioned from PROIN® Chewable Tablets to PROIN ER™.

Secondary Variable: The owner assessment of the control of UI at the end of the 28 day study period was "improved" for 13 (12.5%) dogs, "stayed the same" for 90 (86.5%) dogs, and "worsened" for 1 dog (1%). When improved and stayed the same were combined for a total of 103 (99.0%) dogs, the proportion was found significantly different from 80% by the binomial test ($p < 0.0001$). The lower bound of the two-sided 95% confidence interval was 97.2%.

The acceptability of each dose during the 28 day study period was recorded by the owner. Dogs voluntarily consumed 11.4% of the doses without food and 70.8% of the doses with a small amount of food; 17.6% of doses were "pilled" by the owner and 0.2% of doses were refused.

Adverse Reactions:

Table II.4. Number and percentage of dogs with adverse reactions in the 180-Day open-label clinical study of PROIN ER™

Adverse Reactions	Total N=119
Emesis	39 (32.8%)
Body weight loss (≥5%)	34 (28.6%)
Hypertension (≥160 mmHg) developed during study[a]	15 (12.6%)
Diarrhea	20 (16.8%)
Proteinuria	16 (13.4%)
Tachycardia (≥160 bpm)	11 (9.2%)
Lethargy	11 (9.2%)
Decreased appetite	10 (8.4%)
Urinary Tract Infection	10 (8.4%)
Elevated Alkaline phosphatase and/or Alanine Aminotransferase	7 (6%)
Hypoglycemia	4 (3.3%)
Hypercalcemia	3 (2.5%)
Increased BUN	2 (1.7%)
Bradycardia (<60 bpm)	2 (1.7%)
Seizures/twitching	2 (1.7%)

[a]There were an additional 21 dogs enrolled with hypertension who remained hypertensive throughout the study.

The most common adverse reactions seen in dogs who were administered PROIN ER™ were emesis, body weight loss, hypertension and diarrhea. During the first week of administration of PROIN ER™, 18 (15%) dogs had reported emesis, diarrhea, or decreased appetite which improved or resolved prior to the Day 21 visit, while other dogs had intermittent emesis or diarrhea throughout the study. Dogs that experienced body weight loss or hypertension generally experienced these reactions throughout the study.

Four deaths occurred during the study. Two deaths were not drug related with one dog euthanized for pulmonary metastasis and one dog for poor quality of life due to hindlimb weakness. Two deaths had no definitive cause determined. One dog had a one-day history of emesis and died at home. Upon necropsy a foreign body was present in the small intestine. The other dog developed polyuria,

polydipsia, and weight loss with a leukocytosis, azotemia, and pyuria. Despite treatment for a urinary tract infection and reported improvement in clinical signs and bloodwork results, the dog died unexpectedly at home 3 weeks later of undetermined cause and no necropsy was performed.

Conclusion: Treatment with PROIN ER™ administered orally once a day at a dose range of 2 - 4 mg/kg was safe and effective for the control of urinary incontinence due to urethral sphincter hypotonus. The most common adverse reactions were emesis, weight loss, hypertension, and diarrhea.

III. TARGET ANIMAL SAFETY

The safety of PROIN ER™ was demonstrated using data from two pharmacokinetic studies (Studies PL-CL012 and PL-CL015, described below). Analysis of the data from these two studies determined that the systemic phenylpropanolamine exposure was similar for dogs administered PROIN ER™ when compared to dogs administered PROIN® Chewable Tablets. Therefore, the safety of PROIN ER™ is established by the safety data for PROIN® Chewable Tablets (NADA 141-324). The data supporting the safety of PROIN® Chewable Tablets is summarized in the Freedom of Information Summary (NADA 141-324), dated August 4, 2011. The two single dose pharmacokinetic studies were conducted using the same twelve female Beagle dogs in both studies, and in the same laboratory under the same post-prandial conditions. The same bioanalytical method was used to measure plasma drug concentrations. The pharmacokinetic data from these twelve dogs were used to compare the post-prandial 24 hour drug exposure of both formulations.

Title: Pivotal Two-Way Oral Bioequivalence Study of Two Phenylpropanolamine HCl Preparations In Beagles; Study Number: PLI-CL012

Study PLI-CL012 was designed as a single dose, two treatment, two period, two sequence crossover study with a 14 day washout period between periods to compare the bioequivalence of PROIN® Chewable Tablets with a phenylpropanolamine oral solution. However, 14 of 24 dogs developed emesis in the fasted state in Period I, so the study was modified to include dosing in a fed state in Period II. A third period was added to the study, where dogs were again dosed in the fed state, following a 16 day washout period. The post-prandial data from the single dose of the PROIN® Chewable Tablet was used in the comparative analysis of PROIN® Chewable Tablets and PROIN ER™.

During Periods II and III, the dogs were fasted overnight for at least 8 hours and then fed 30 minutes prior to dosing. The dogs were administered a single dose of 50 mg PROIN® Chewable Tablets resulting in doses ranging from 2.24 - 2.63 mg/kg based on body weight, which is slightly higher than the maximum labeled dose of 2 mg/kg. Blood samples were obtained prior to dosing and at 15 minutes, 30 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours following dosing. Plasma drug concentrations were measured using a validated LC-MS/MS method.

In order to compare the post-prandial drug exposure over a 24 hour period from the twice daily administration of PROIN® Chewable Tablets to the once daily administration of PROIN ER™, the post-prandial single dose data from PLI-CL012 were simulated to estimate the drug exposure following multiple doses. The following

equation was used to calculate the plasma concentrations of PROIN® Chewable Tablets after 4 doses (doses administered once every 12 hours):

C_{12hr}*EXP (-(T_2-T_1)*lambda z)

Where C_{12hr} is the plasma concentration at 12 hours after a single dose, T_2-T_1 is the difference in time between the two sampling time points, and lambda z is the slope of the terminal elimination phase after a single dose for each dog. The plasma concentrations at Doses 2 - 4 were the summation of the residual drug from the previous dosing interval plus the new dose. There was minor accumulation at steady state for each dog, with accumulation ratios ranging from 1.0 - 1.19. A non-compartmental analysis (NCA) with uniform weighting was performed (Phoenix WinNonlin version 6.4) using the simulated plasma concentrations to obtain the maximum concentration (C_{max}), the area under the concentration versus time curve from 0-24 hours (AUC_{0-24}), and the area under the concentration versus time curve at steady state (AUC_{ss}).

Title: Pivotal Two-Way Crossover Study Comparative Pharmacokinetics of Phenylpropanolamine HCl Extended Release Tablets in Fed and Fasted Beagles; Study Number: PLI-CL015

Study PLI-CL015 was a two treatment, two sequence, two period crossover study with a washout period of 14 days comparing the relative bioavailability of PROIN ER™ under fed and fasted conditions. Prior to dosing, dogs were fasted overnight for at least 6 hours prior to dosing. For the fed phase of the study, the dogs were given their daily ration 30 minutes before dosing and allowed to consume the pre-dose ration until approximately 3 minutes before dosing occurred. The dogs were administered a single dose of 38 mg PROIN ER™ resulting in doses ranging from 3.12 to 3.81 mg/kg based on body weight, which is slightly under the maximum labeled dose of 4 mg/kg. Blood samples were obtained prior to dosing and at 15 minutes, 30 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours following dosing. Plasma drug concentrations were measured using a validated LC-MS/MS method. An NCA with uniform weighting was performed (Phoenix WinNonlin version 6.4) to obtain the maximum concentration (C_{max}), the area under the concentration versus time curve from 0-24 hours (AUC_{0-24}), and the area under the concentration versus time curve at steady state (AUC_{ss}).

Pharmacokinetic Data Simulation for Studies PLI-CL012 and PLI-C015

Because both studies were conducted at either a dose above (Study PLI-CL012) or below (Study PLI-CL015) the maximum labeled dose, the post-prandial steady state drug exposure following 2 mg/kg every 12 hours of PROIN® Chewable Tablets and 4 mg/kg dose every 24 hours of PROIN ER™ was simulated using Non-parametric Superposition (Phoenix version 6.4 software). An NCA with uniform weighting was performed (Phoenix WinNonlin version 6.4) to obtain the maximum concentration (C_{max}), the area under the concentration versus time curve from 0-24 hours (AUC_{0-24}), and the area under the concentration versus time curve extrapolated at steady state (AUC_{ss}) for the simulations.

Comparative Analysis of Pharmacokinetic Data

An ANOVA analysis was performed for C_{max} at steady state (C_{maxss}), AUC $_{0-24}$, AUC_{ss}, C_{max}/Dose, AUC $_{0-24}$/Dose, and AUC_{ss}/Dose from both studies, using Proc MIXED in SAS 9.4. The parameters were log transformed prior to analysis. The fixed effect was formulation, and the random effect was subject within formulation. The alpha was 0.10. The ratio of the parameters obtained from PROIN ER™ to those from PROIN® Chewable Tablets, and the corresponding 90% Confidence Intervals (CIs), were generated based on the statistical model. The parameters were dose normalized for the total dose administered in 24 hours (50 mg for PROIN® Chewable Tablets and 38 mg for PROIN ER™) to evaluate the difference in exposure based on the total dose administered. The results as summarized in Table III.1 demonstrate that at the doses administered in their respective studies, the steady state drug exposure of the PROIN ER™ administered once a day was lower than that of PROIN® Chewable Tablets administered twice a day.

Table III.1: ANOVA results of PROIN® Chewable Tablets versus PROIN ER™ using observed and simulated data; n=12, Dose= 50 mg for PROIN® Chewable Tablets and 38 mg for PROIN ER™

Parameter	Units	IR geo mean	ER geo mean	Ratio of ER to IR	Lower 90% CI	Upper 90% CI
C_{maxss}	ng/mL	861.52	626.72	0.73	62.11	85.21
AUC $_{0-24}$	h*ng/mL	7650.59	5158.03	0.67	58.20	78.10
AUC_{ss}	h*ng/mL	7998.56	5297.33	0.66	56.68	77.38
C_{maxss}/Dose	ng/mL/mg	17.23	16.49	0.96	81.73	112.14
AUC $_{0-24}$/Dose	h*ng/mL/mg	153.01	135.74	0.89	76.58	102.76
AUC_{ss}/Dose	h*ng/mL/mg	159.97	139.40	0.87	74.58	101.82

IR=Immediate Release PROIN® Chewable Tablets
ER=Extended Release PROIN ER™
ER/IR=PROIN ER™/PROIN® Chewable Tablets
Geo mean=Geometric Mean
CI=Confidence Interval

The above analysis was repeated using the post-prandial steady state simulated data of administration of the 2 mg/kg dose every 12 hours of PROIN® Chewable Tablets and 4 mg/kg dose every 24 hours of PROIN ER™ (see Table III.2). The simulation of the single 4 mg/kg dose of PROIN ER™ resulted in a slightly higher C_{max}, but the overall drug exposure (as represented by AUC $_{0-24}$ and the AUC_{ss}) of a single 4 mg/kg dose is less than two 2 mg/kg doses of PROIN® Chewable Tablets.

Table III.2: ANOVA analysis of the Non-parametric Superposition simulation for 2 mg/kg every 12 hours for PROIN® Chewable Tablets and 4 mg/kg every 24 hours for PROIN ER™

Parameter	Units	IR geo mean	ER geo mean	Ratio of ER to IR	Lower 90% CI	Upper 90% CI
C_{maxss}	ng/mL	707.30	726.63	1.03	88.41	119.38
AUC_{0-24}	h*ng/mL	6492.18	5980.33	0.92	85.08	99.74
AUC_{ss}	h*ng/mL	7061.59	6141.83	0.87	80.70	93.74

IR=Immediate Release PROIN® Chewable Tablets
ER=Extended Release PROIN ER™
ER/IR=PROIN ER™/PROIN® Chewable Tablets
Geo mean=Geometric Mean
CI=Confidence Interval

Clinical Observations: The only clinically relevant findings were emesis and ventral abdominal hyperemia. There was one incident of dorsal midline piloerection.

Conclusion: A statistical analysis using observed and simulated data to compare the postprandial pharmacokinetic data of PROIN ER™ and PROIN® Chewable Tablets resulted in confidence limits that were consistent with equal or lower oral bioavailability for PROIN ER™ when administered once daily versus PROIN® Chewable Tablets when administered twice daily. Because the systemic phenylpropanolamine exposure in dogs administered 38 mg PROIN ER™ once daily was similar to dogs administered 50 mg PROIN® Chewable Tablets twice daily, the safety of PROIN ER™ is supported by the safety data for PROIN® Chewable Tablets (NADA 141-324). These data support the safety of PROIN ER™ when administered at a dose of 2 - 4 mg/kg once daily for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

IV. 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 NADA.

V. USER SAFETY

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

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that PROIN ER™, 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

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional veterinary expertise is required to diagnose urinary incontinence, to determine that the dog's condition is not due to other medical or surgical reasons, and to monitor the safe use of the product, including management of any adverse reactions.

B. EXCLUSIVITY

PROIN ER™, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of PROIN ER™.

C. PATENT INFORMATION

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