

Make your dog feel like  
a **Superhero** with the power of  
Urinary Continence Control.



**PROIN ER™**

(phenylpropranolamine hydrochloride  
extended-release tablets)

**PROIN®**

(phenylpropranolamine hydrochloride)  
Chewable Tablets



When the problem is **Urethral Sphincter Hypotonus**,  
you now have two choices:

**PROIN ER™** (*phenylpropanolamine hydrochloride  
extended-release tablets*)

**PROIN®** (*phenylpropanolamine hydrochloride*)  
*Chewable Tablets*

FDA approved for control of urinary incontinence  
due to urethral sphincter hypotonus

Up to **20%** of spayed female dogs  
may develop urinary  
incontinence.<sup>1</sup>

Effective treatment  
for control of canine urinary  
incontinence

Inappropriate urination is a common  
problem for dogs, especially as they age.  
Spayed female dogs tend to be more prone  
to urinary incontinence. When the cause of  
urinary incontinence is urethral sphincter  
hypotonus, PROIN® (phenylpropanolamine  
hydrochloride) Chewable Tablets and  
PROIN ER™ (phenylpropanolamine  
hydrochloride extended-release tablets)  
can help.

#### References

1. Von Goethem B, Schaeffers-Okkens A, Kirpensteijn J. Making a rational choice between ovariectomy and ovari hysterectomy in the dog: a discussion of the benefits of either technique. *Vet Surg* 2006; 35:136-143.

**IMPORTANT SAFETY INFORMATION:** For oral use in dogs only. Not for human use. Keep out of reach of children. If accidentally ingested by humans, contact a physician immediately.

The most commonly reported side effects were vomiting, loss of appetite, diarrhea, excessive salivation, agitation, tiredness, vocalization, confusion, increased water consumption, weight loss, weakness, fever, panting, and reversible changes in skin color (flushing or bright pink). Abnormal gait, seizures or tremors, as well as liver enzyme elevations, kidney failure, blood in urine and urine retention have been reported. In some cases death, including euthanasia has been reported. Sudden death was sometimes preceded by vocalization or collapse.

Instances of dogs chewing through closed vials of PROIN® and eating the

vial contents have been reported, in some cases resulting in overdose. Keep the product in a secured storage area out of the reach of pets in order to prevent accidental ingestion or overdose, as dogs may willingly consume more than the recommended dosage of PROIN® Chewable tablets or PROIN ER™ tablets. Contact your veterinarian immediately if the dog ingests more tablets than prescribed or if other pets ingest PROIN Chewable tablets or PROIN ER tablets.

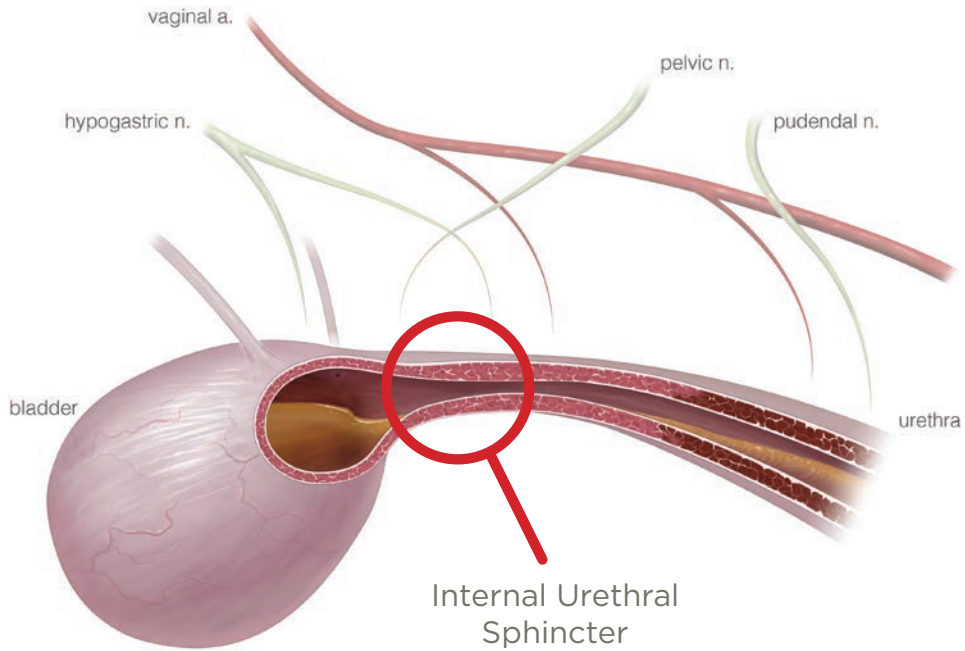
PROIN and PROIN ER may cause elevated blood pressure and should be used with caution in dogs with pre-existing heart disease, high blood pressure, liver disease, kidney insufficiency, diabetes, glaucoma, and other conditions associated with high blood pressure. Dogs may transition from PROIN Chewable Tablets to PROIN ER without

a break in administration. However, do not alternate PROIN ER with PROIN Chewable Tablets because the effectiveness and safety of interchangeable use have not been evaluated.

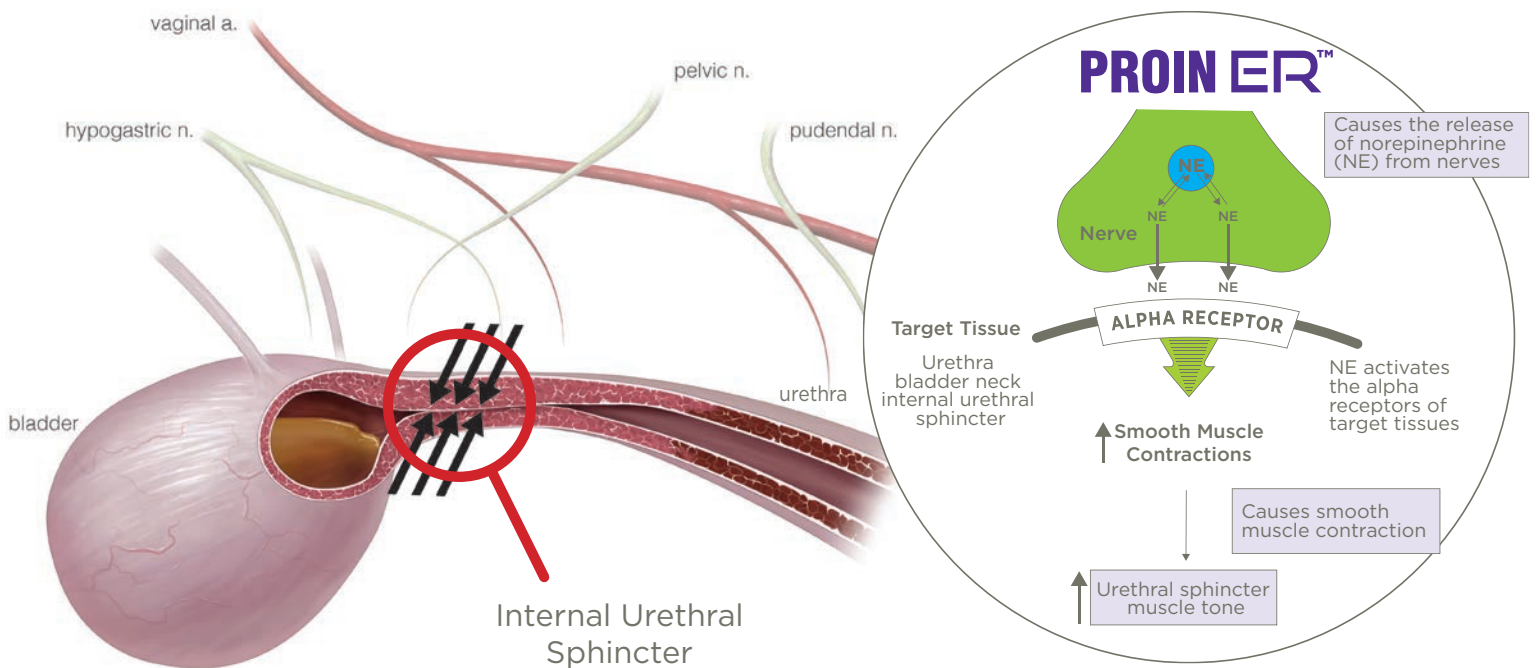
The safe use of PROIN and PROIN ER in dogs used for breeding purposes, during pregnancy or in lactating bitches, has not been evaluated. Contact your veterinarian if you notice restlessness or irritability, loss of appetite, the incontinence persists or worsens, or any other unusual signs. See prescribing information for complete details regarding adverse events, warning and precautions or visit [prnpharmaceutical.com](http://prnpharmaceutical.com).

# PROIN ER™ And PROIN® Work by Increasing Urethral Sphincter Muscle Tone to Help Prevent Urinary Leakage.

## Urethral Sphincter **Without** PROIN ER or PROIN



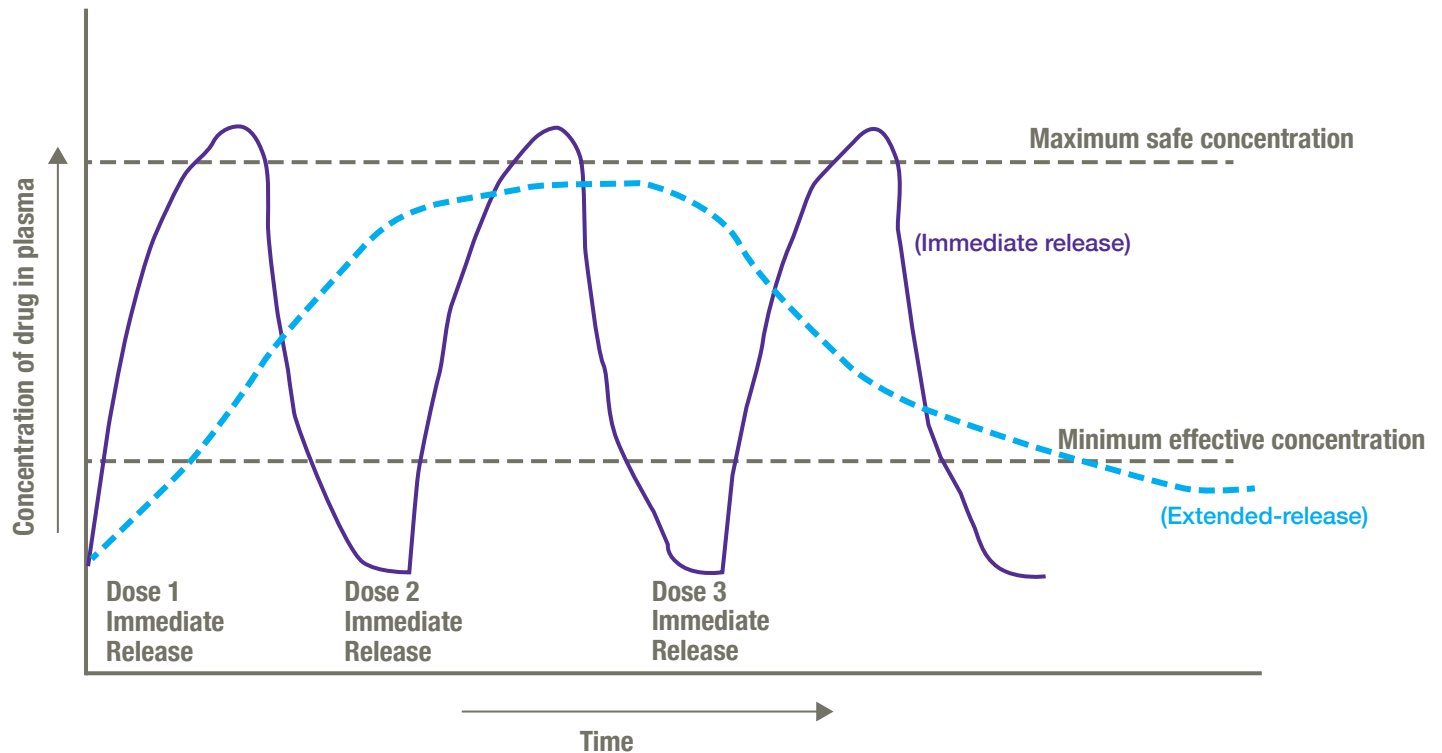
## Urethral Sphincter **With** PROIN ER or PROIN



**PROIN ER™** (phenylpropanolamine hydrochloride extended-release tablets) & **PROIN®** (phenylpropanolamine hydrochloride Chewable Tablets)

Different absorption rates, **equally effective**

## Example of How Extended and Immediate Release Formulations Release Drugs for Absorption\*



PROIN and PROIN ER provide different absorption rates to ensure that effective dosages can be administered either in multiple dosages throughout the day (PROIN) or once per day (PROIN ER). PROIN chewable tablets release the medication into the dog's system immediately, with levels of absorption that vary over time—multiple dosages provide the effective daily dosage prescribed.

PROIN ER, with patented extended-release technology, provides steady absorption while maintaining a safe and effective concentration of the medication in a single daily dose. Both forms are equally effective when administered as prescribed.



Dogs may transition from PROIN Chewable Tablets to PROIN ER without a break in administration. However, do not alternate PROIN ER with PROIN Chewable Tablets because the effectiveness and safety of interchangeable use have not been evaluated.

\* For concept illustration only, not actual release profiles of PROIN.

**ONCE-A-DAY**

*“P is for PROIN, ER is for Extended-Release”*

# PROIN ER™ *(phenylpropanolamine hydrochloride extended-release tablets)*



PROIN ER™ (phenylpropanolamine hydrochloride extended-release tablets) provides the same proven efficacy as PROIN® (phenylpropanolamine hydrochloride) in extended-release tablets **for once-a-day dosing. Our patented extended-release technology provides a controlled release mechanism that provides steady absorption.**

**PROIN ER is:**

***Convenient***

Given with food, **a single dose per day simplifies treatment**

***Innovative***

**Patented release technology provides controlled release that ensures steady absorption**

***Easy to Administer***

Chewable, liver-flavored tablets improve compliance

***Easy to Prescribe***

Four dosing strengths based on body weight provide simplicity

***FDA Approved***

FDA approved for control of urinary incontinence due to urethral sphincter hypotonus in dogs



Available in 30 ct. bottles



**The controlled release mechanism of PROIN ER provides for steady absorption.**

**PROIN ER** comes in four sizes for dosing:

- 18 mg: 10-20 lbs.
- 38 mg: 21-40 lbs.
- 74 mg: 41-80 lbs.
- 145 mg: 81-125 lbs.

Administer PROIN ER with food

# PROIN ER™ (phenylpropanolamine hydrochloride extended-release tablets)

## Study Summary



**82.2%** of doses voluntarily consumed when given without or with a small amount of food.<sup>2</sup>

Treatment that works, in a form that pets will take.

### Effectiveness, Safety and Oral Acceptability Study of PROIN ER™ (phenylpropanolamine hydrochloride extended-release tablets)

The extended-release formulation of phenylpropanolamine was evaluated in an open-label clinical field study sponsored by Pegasus Laboratories.

#### Method:

- Multi-center clinical field study
- 119 client-owned dogs previously diagnosed with urinary incontinence (UI) due to Urethral Sphincter Mechanism Incompetence (USMI) were administered PROIN® Chewable Tablets and considered controlled for their incontinence. Of these, **104 were evaluated for effectiveness.**
- The pet owner recorded the number of urinary accidents during the baseline period of dosing with PROIN® Chewable Tablets and during the first 28 days of dosing with PROIN ER. The ratio of average daily incidence of UI was calculated by comparing the baseline dosing period of PROIN Chewable Tablets (Day -7 to Day -1) with the Day 21 to Day 27 dosing period of PROIN ER tablets.

#### Results:

Seventy-five of 104 dogs had no change from baseline (well controlled for signs of urinary incontinence). **Nineteen dogs showed improvement over baseline.**

**99%** of owners in the study, when asked on Day 28, assessed their dog as "improved" or "stayed the same."

**Acceptability** was recorded by the pet owners; 11.4% of the doses were consumed without food and 70.8% of the doses were accepted with a small amount of food.

**Treatment with PROIN ER tablets** administered once-a-day at dose range of 2-4 mg/kg orally was **safe & effective for the control of urinary incontinence due to urethral sphincter hypotonus.**

**“P is for PROIN, PROIN is for Pee!”**

# PROIN<sup>®</sup> (phenylpropanolamine hydrochloride) Chewable Tablets



In a six-month study, PROIN achieved  
**98.1%** owner satisfaction  
for the control of  
urinary incontinence.<sup>3</sup>

### Common clinical signs of urinary incontinence in dogs

- Dripping or leaking urine
- Excessive licking of genital area
- Red, irritated skin around genital area
- Increased frequency of need to urinate
- Wetting the bed or sleeping area
- Inappropriate urination in the house

**PROIN<sup>®</sup>** can help control these signs by improving muscle tone in the urethral sphincter to prevent urinary accidents.

### PROIN is:

#### **Proven**

FDA approved for control of urinary incontinence due to urethral sphincter hypotonus

#### **Precise**

Scored tablets are available in three strengths for accurate dosing

#### **Pet-Accepted**

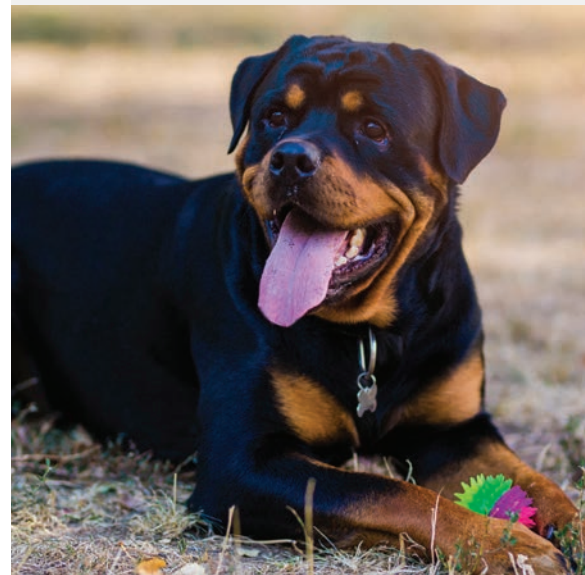
Chewable, liver-flavored tablets dogs love



Available in 60 ct. and 180 ct. bottles



For more than a decade, veterinarians have trusted PROIN to help strengthen urethral sphincter muscle control. PROIN is FDA approved.



### References

1. Pegasus Laboratories, Inc. (2019). Freedom of Information (FOI) Summary for PROIN ER (phenylpropanolamine hydrochloride extended-release tablets) Dogs: US, (NADA 141-517). Center for Veterinary Medicine (CVM).
2. Pegasus Laboratories, Inc. (2011). Freedom of Information (FOI) Summary for PROIN (phenylpropanolamine hydrochloride) Chewable Tablets Dogs: US, (NADA 141-334). Center for Veterinary Medicine (CVM). (Retrieved from <https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadF0i/881>).

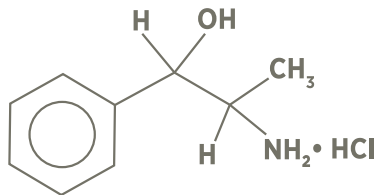
# PROIN ER<sup>TM</sup>

## (phenylpropanolamine hydrochloride extended-release tablets)

For oral use in dogs only

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

**DESCRIPTION:** PROIN ER (phenylpropanolamine hydrochloride extended-release tablets) is a sympathomimetic amine closely related to ephedrine. Phenylpropanolamine hydrochloride (PPA) is the nonproprietary designation for benzenemethanol,  $\alpha$ -(1-aminoethyl)-hydrochloride, (R\*, S\*), ( $\pm$ ). The empirical formula is  $C_9H_{13}NO \cdot HCl$  and the molecular weight is 187.67. It is a white crystalline compound having a slight aromatic odor. PPA is freely soluble in water and alcohol but is practically insoluble in ether, benzene and chloroform. The chemical structure of phenylpropanolamine hydrochloride is:



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

**DOSAGE AND ADMINISTRATION:** The recommended dosage is 2 to 4 mg/kg (0.9 to 1.8 mg/lb) of body weight once daily according to Table 1 below. Administer PROIN ER with food (see **Clinical Pharmacology**). **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 1. Dose Administration<sup>a</sup>

Body weight in pounds	PROIN ER
10-20	18 mg
21-40	38 mg
41-80	74 mg
81-125 <sup>b</sup>	145 mg

<sup>a</sup>Body weight should be rounded to the nearest pound.

<sup>b</sup>Dogs exceeding 125 lbs should receive the appropriate combination of tablets to achieve the recommended dosage.

Dogs may transition from PROIN<sup>®</sup> Chewable Tablets to PROIN ER without a break in administration. However, do not alternate PROIN ER with PROIN Chewable Tablets because the effectiveness and safety of interchangeable use have not been evaluated.

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

Keep PROIN ER in a secured location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

**PRECAUTIONS:** Proin ER may mask signs of incontinence due to urinary tract infection. PROIN ER is not effective in dogs with incontinence due to neurologic disease or malformations.

PROIN ER may cause hypertension; therefore, use with caution in dogs with pre-existing heart disease, hypertension, liver disease, kidney insufficiency, diabetes, glaucoma, and conditions with a predilection for hypertension.

Use with caution in dogs receiving sympathomimetic drugs, tricyclic antidepressants, or monoamine oxidase inhibitors as increased toxicity may result. Use with caution in dogs administered halogenated gaseous anesthetics as this may increase the risk of cardiac arrhythmias.

A laboratory study on human blood revealed that phenylpropanolamine (PPA) used in conjunction with aspirin may potentiate decreased platelet aggregation.<sup>1</sup>

PROIN ER may cause increased thirst; therefore, provide dogs with ample fresh water.

The safe use of PROIN ER has not been evaluated in dogs that are intended for breeding, or that are pregnant or lactating.

**ADVERSE REACTIONS:** Adverse Reactions are listed below for both PROIN ER (NADA Number 141-517) and PROIN Chewable Tablets (NADA 141-324).

PROIN ER (NADA 141-517)

In the open-label clinical study involving 119 dogs administered PROIN ER once a day for 180 days, the following adverse reactions were observed.

Table 2. Number and percentage of dogs with adverse reactions in the 180-day open-label clinical study for PROIN ER

Adverse Reactions	Total N=119
Emesis	39 (32.8%)
Body weight loss ( $\geq 5\%$ )	34 (28.6%)
Hypertension ( $\geq 160$ mmHg) developed during study <sup>a</sup>	15 (12.6%)
Diarrhea	20 (16.8%)
Proteinuria	16 (13.4%)
Tachycardia ( $\geq 160$ 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 (6.0%)
Hypoglycemia	4 (3.3%)
Hypercalcemia	3 (2.5%)
Increased BUN	2 (1.7%)
Bradycardia ( $< 60$ bpm)	2 (1.7%)
Seizures/twitching	2 (1.7%)

<sup>a</sup>There were an additional 21 dogs enrolled with hypertension who remained hypertensive throughout the study.

During the first week of administration of PROIN ER, 15% of dogs had reported emesis, diarrhea, or decreased appetite which improved or resolved prior to the Day 21 visit.

Four deaths occurred during the study. One dog was euthanized for pulmonary metastasis and one dog for poor quality of life due to hindlimb weakness. One dog had emesis and died at home; upon necropsy a foreign body was present in the small intestine. The fourth dog had been treated for a urinary tract infection three weeks prior to sudden death of undetermined cause.

PROIN Chewable Tablets (NADA 141-324):

Table 3 below includes the most common adverse reactions observed in the masked, placebo-controlled 28-day clinical study involving 123 PROIN Chewable Tablet-treated dogs and 61 placebo-treated dogs. In addition, one dog exhibited disorientation, nervousness, a 7.7% loss of body weight, and hypertension with proteinuria. A second dog exhibited restless behavior, lethargy, a 2.8% body weight loss, and proteinuria.

Table 3. Number and percentage of dogs with adverse reactions in the 28-day placebo-controlled clinical study for PROIN Chewable Tablets

Adverse Reactions	PROIN-treated (N=123)	Placebo-treated (N=61)
Emesis	20.3%	8.2%
Hypertension ( $\geq 160$ mmHg) <sup>a</sup>	19.5%	14.7%
Anorexia	16.3%	3.3%
Body weight loss ( $> 5\%$ ) <sup>b</sup>	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%

<sup>a</sup>One or more systolic blood pressure readings of  $\geq 160$  mmHg.

<sup>b</sup>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.

One-hundred fifty-seven dogs continued into the 6-month open-label clinical study for PROIN Chewable Tablets. The most common adverse reactions are listed in Table 4 below. In addition, one dog exhibited progressively worsening hypertension with proteinuria. Five dogs enrolled in the study with pre-existing heart disease. Of these, one dog developed systolic failure with an unknown relation to treatment.

Table 4. Number and percentage of dogs with adverse reactions in the 6-month open-label clinical study for PROIN Chewable Tablets

Adverse Reactions	Total N=125
Hypertension ( $\geq 160$ mmHg) <sup>a</sup>	34.6%
Body weight loss ( $> 5\%$ )	24.8%
Emesis	19.7%
Proteinuria	15.3%
Anorexia	10.2%
Diarrhea	6.4%
Lethargy	5.7%
Anxiety/aggression/behavior change	5.7%

<sup>a</sup> Percent of dogs with systolic blood pressures of  $\geq 160$  mmHg on day -7 were 30.2% and on day 0 were 33.3%.

*Post Approval Experience for PROIN Chewable Tablets (2015):*

The following adverse reactions are based on voluntary, post approval reporting for PROIN Chewable Tablets (2015). Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The signs reported are listed in decreasing order of reporting frequency by body system:



Gastrointestinal: Emesis, anorexia, diarrhea, hypersalivation  
 Behavioral: Agitation, lethargy, vocalization, confusion  
 General body system: Polydipsia, weight loss, weakness, fever  
 Respiratory: Panting  
 Dermatological: Erythema, piloerection  
 Hepatic: Elevated serum alanine aminotransferase (ALT), elevated serum alkaline phosphatase (ALP)  
 Neurologic: Ataxia, seizures, tremors  
 Renal/Urinary: Renal failure, hematuria, urinary retention  
 Cardiovascular: Tachycardia, hypertension, bradycardia, arrhythmias  
 Sensory: Ophthalmic disorders, mydriasis and eye redness

In some cases, death, including euthanasia, has been reported. Sudden death was sometimes preceded by neurologic signs, vocalization, or collapse. A necropsy of one dog revealed subarachnoidal and intraventricular hemorrhage in the brain.

The following signs have been reported more often with a dose higher than the recommended dosage: agitation, arrhythmia, bradycardia, erythema, fever, hypersalivation, hypertension, lethargy, mydriasis, panting, piloerection, tachycardia, tremor, and urinary retention.

**Contact Information** For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Pegasus Laboratories at 1-800-874-9764. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

**INFORMATION FOR DOG OWNERS:**

Always follow the dosage instructions for PROIN ER provided by your veterinarian. Give PROIN ER with food and do not split or crush the tablet. Monitor your dog after giving PROIN ER to be sure all of it was consumed. If you have difficulty giving PROIN ER, contact your veterinarian.

PROIN ER may cause increased thirst; therefore, provide dogs with ample fresh water.

If you forget to give your dog a dose, then resume dosing at the next scheduled dose. Keep PROIN ER in a secured location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Contact your veterinarian immediately if the dog ingests more tablets than prescribed or if other pets ingest PROIN ER. In the case of accidental ingestion by humans, contact a physician immediately.

Contact your veterinarian if you notice restlessness, irritability, loss of appetite, the incontinence persists or worsens, or any other unusual signs.

Consult your veterinarian before administering PROIN ER with any other medications.

**CLINICAL PHARMACOLOGY:**

Phenylpropranolamine is a chemical analogue of the endogenous sympathomimetic amines. It is an alpha-adrenergic agent which has been reported to increase urethral tone in dogs.<sup>2</sup> Its mechanism of action is not well determined, but it is believed to cause the release of norepinephrine by indirectly stimulating both the alpha and beta-adrenergic receptors of the smooth muscle to increase smooth muscle tone of the urethra, bladder neck, and the internal urethral sphincter.<sup>3,4</sup>

In a crossover pharmacokinetic study of PROIN ER in fed and fasted dogs, post-prandial drug administration was associated with approximately a 23% increase in the maximum plasma concentration (C<sub>max</sub>), but the area under the concentration vs time curve to the last quantifiable concentration (AUC<sub>last</sub>) was similar in both fed and fasted states. The small decrease in the post-prandial AUC<sub>last</sub> appeared to be attributable to the corresponding increase in the terminal elimination rate constant under the fed conditions. The time to C<sub>max</sub> (T<sub>max</sub>) was more variable in the fasted state, ranging from 1.5 to 8 hours compared to 2 to 6 hours for the fed state. The elimination half-life (t<sub>1/2</sub>) was also more variable in the fasted state, ranging from 3.89 to 10.35 hours compared to 2.98 to 7.81 hours for the fed state.

**EFFECTIVENESS:**

Effectiveness of PROIN ER was demonstrated in a multi-center, prospective, open-label, 6-month study in client-owned dogs of various breeds. In this study, 119 dogs (113 spayed females and 6 neutered males, aged 1-16 years and weighing 4.9-81.8 kg) who were considered well controlled for signs of urinary incontinence (UI) while receiving PROIN Chewable Tablets for at least 30 days prior to study start were enrolled in the study. Of these dogs, 104 were evaluated for effectiveness. The owners continued to administer PROIN Chewable Tablets twice a day and recorded episodes of UI during a baseline period (Day - 7 through Day -1). After the baseline period, the owners transitioned to administration of PROIN ER once a day, at the labeled dose (see **Dosage and Administration**), and recorded urinary accidents for 28 days.

The primary variable was the ratio of average daily incidence of UI during the 7 days preceding the Day 28 clinic visit compared to the baseline period. It was concluded that PROIN ER was effective for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

**Table 5: 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 secondary outcome variable was owner assessment of the control of UI at the end of the 28 day study period. The owner assessment was "improved" for 13 (12.5%) dogs, "stayed the same" for 90 (86.5%) dogs and "worsened" for 1 dog (1%).

**ANIMAL SAFETY:**

The safety of PROIN ER was established based on the safety data from PROIN Chewable Tablets (see below) and a comparative analysis of pharmacokinetic (PK) data for PROIN ER and PROIN Chewable Tablets. The statistical analysis of observed and simulated post-prandial pharmacokinetic

data resulted in confidence limits consistent with equal or lower oral bioavailability for PROIN ER when administered once daily versus PROIN Chewable Tablets when administered twice daily. Therefore, the safety data from PROIN Chewable Tablets could be applied to PROIN ER. Emesis and hyperemia of the ventral abdomen were observed during the PK studies.

**Target Animal Safety Study (PROIN Chewable Tablets, NADA 141-324)**

In a target animal safety study, PROIN Chewable Tablets were administered to 32 healthy male and female Beagle dogs at 0, 2, 6 and 10 mg/kg of body weight (0, 1, 3 and 5 times the recommended dose; 8 dogs per group) twice daily for 26 consecutive weeks. The most pronounced finding was a dose-dependent increase in blood pressure. Mean systolic blood pressure was increased in all PPA-treated groups compared to the control, but mean values for all 4 groups were within the normal range. Mean diastolic and mean MAP (mean arterial pressure) were higher in the 3X and 5X groups, and in the 1X males. Dogs in the 3X and 5X groups had more individual systolic, diastolic, and MAP values above the normal range than the control group dogs. A dose-dependent decrease in heart rate was observed in the 3X and 5X dogs. In the 0, 1, 3, and 5X groups, 5%, 34%, 44%, and 40% of the total number of heart rates obtained from electrocardiograms for each group over the course of the study were below the normal range (70-120 beats per minute), with the lowest value being 51 bpm in 4 of the 1X group dogs. One dog in each of the 1X and 5X groups had an elevated heart rate between 150-180 beats per minute on at least 2 of the 13 physical exams. One dog in each of the 1X and 3X groups developed gallop heart sounds after treatment began that were noted in 12 of 13 and 6 of 13 physical exams respectively. Dogs in the PPA-treated groups exhibited anxious/restless behavior more frequently than the control group. One dog each in the 1X and 3X groups were responsible for the majority of the observations. A decline in mean body weight and body condition was observed in females in all 4 groups, including the control. One female in the 1X group lost 33% body weight. Emesis and loose stool occurred in a dose-related fashion, and most of the emesis episodes took place within 1 hour of dosing. Mean platelet counts were higher in at least one of the PPA-treated groups, with individual values up to 1.4X the upper limit of normal (ULN) in the 3X and 5X groups. The 3X and 5X groups had higher mean serum ALT values compared to the control. Mean ALT was within the normal range for all 4 groups. There were more dogs with ALT levels above the normal range in the 3 PPA-treated groups compared to the control, but increased values were transient and less than 1.8X ULN. All dogs had ALT values in the normal range at the conclusion of the study.

**Tolerance study (PROIN Chewable Tablets, NADA 141-324)**

In the separate tolerance study, 6 healthy female Beagle dogs were administered PROIN Chewable Tablets at 20 mg/kg body weight (10 times the recommended dose) twice daily for 21 consecutive days. Mean systolic blood pressure was increased in the 10X group compared to the control, but mean values were within the normal range for both groups. Mean diastolic pressures were above the normal range on days 7 and 21 for the 10X group, and day 14 for the control. The 10X dogs had hypertensive mean MAP values on days 7 and 21, whereas the control dog mean MAP values were in the normal range. There was a trend in 10X dogs for lower heart rates following initiation of PPA treatment. Four of 6 dogs in the 10X group had heart rates below the normal range on day 7, whereas none of the control dogs did. The 10X group dogs had increased hematocrit, hemoglobin, RBC counts, urine specific gravity, and water intake consistent with transient, sub-clinical dehydration that occurred shortly after PPA treatment was started. All 6 dogs in the 10X group developed emesis during the treatment period, whereas only 1 of the control dogs did. Most of the emesis episodes took place within 1 hour of dosing. Mean platelet counts were also higher in 10X dogs on all 3 exam days; mean values were above the normal range on day 7, with individual values up to 1.5X ULN. The 10X group had a higher mean serum ALT value on day 7 than the control. Mean ALT values for both groups were in the normal range on all 3 exam days, but 2 dogs in the 10X group had ALT values up to 1.4X ULN on day 7; these elevated values were transient, and all dogs had normal ALT values on days 14 and 21.

For either study, there was no evidence of chronic hypertension-induced target organ damage; there were no clinical findings attributable to PPA on the ophthalmic exams, electrocardiogram evaluation, or gross necropsy and histopathology.

**STORAGE:** Store at controlled room temperature 20-25°C (68-77°F), excursions permitted between 15-40°C (59-104°F).

**HOW SUPPLIED:** PROIN ER tablets contain 18, 38, 74 or 145 mg phenylpropranolamine hydrochloride per tablet. PROIN ER is packaged in bottles containing 30 or 90 tablets.

**REFERENCES:**

- Watson R, et al. Ephedra alkaloids inhibit platelet aggregation. Blood coagulation and Fibrinolysis, 2010, 21:266-271.
- Richter K.P., Ling G.V. Clinical response and urethral pressure profile changes after phenylpropranolamine in dogs with primary sphincter incompetence. JAVMA, Vol. 187, No 6, September 15, 1985. 605-611.
- Scott, L., Leddy M. and Bernay, F. Evaluation of phenylpropranolamine in the treatment of urethral sphincter mechanism incompetence in the bitch. J. Small Anim. Pract. 2002;43(11): 493-6.
- Noel, S., et al. Combined pharmacokinetic and urodynamic study of the effects of oral administration of phenylpropranolamine in female Beagle dogs. Vet. Journal, 2010; 184(2): 201-207.

**Approved by FDA under NADA #141-517**

PROIN ER is a trademark of Pegasus Laboratories, Inc.

01/2019

**Manufactured By:**  
**Pegasus Laboratories, Inc.**  
**Employee-Owned**  
**Pensacola, Florida 32514, USA**  
**Manufactured in the USA**

# PROIN<sup>®</sup>

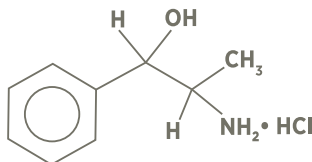
(phenylpropranolamine hydrochloride)

Chewable Tablets

For oral use in dogs only

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

**DESCRIPTION:** PROIN (phenylpropranolamine hydrochloride) is a sympathomimetic amine closely related to ephedrine. Phenylpropranolamine hydrochloride (PPA) is the nonproprietary designation for benzenemethanol,  $\alpha$ -(1-aminoethyl)-, hydrochloride, (R\*, S\*)-, ( $\pm$ ). The empirical formula is  $C_9H_{13}NO \cdot HCl$  and the molecular weight is 187.67. It is a white crystalline compound having a slight aromatic odor. PPA is freely soluble in water and alcohol but is practically insoluble in ether, benzene and chloroform. The chemical structure of phenylpropranolamine hydrochloride is:



**Indication:** PROIN is indicated for the control of urinary incontinence due to urethral sphincter hypotonus in dogs.

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

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

**Precautions:** PROIN may cause increased thirst; therefore, provide ample fresh water.

Overdose has been associated with dogs chewing through closed bottles of PROIN and consuming multiple tablets. Therefore, it is important to store PROIN Chewable Tablets out of reach of dogs and other pets in a secured location.

Use in dogs with incontinence due to a urinary tract infection will mask symptoms. PROIN is not effective in dogs with incontinence due to neurologic disease or malformations.

PROIN may cause hypertension; therefore, use with caution in dogs with pre-existing heart disease, hypertension, liver disease, kidney insufficiency, diabetes, glaucoma, and conditions with a predilection for hypertension. Use with caution in dogs receiving sympathomimetic drugs, tricyclic antidepressants, or monoamine oxidase inhibitors as increased toxicity may result. Use with caution in dogs administered halogenated gaseous anesthetics as this may increase the risk of cardiac arrhythmias.

A laboratory study on human blood revealed that PPA used in conjunction with aspirin may potentiate decreased platelet aggregation.<sup>1</sup>

The safe use of PROIN in dogs used for breeding purposes, during pregnancy or in lactating bitches, has not been evaluated.

**Adverse Reactions "Pre Approval Experience":** A placebo-controlled clinical study involving 123 PROIN-treated dogs and 61 placebo-treated dogs was conducted for 28 days. The most common adverse reactions are shown in Table 1 below. In addition, one dog exhibited disorientation, nervousness, a 7.7% loss of body weight, and hypertension with proteinuria. A second dog exhibited restless behavior, lethargy, a 2.8% body weight loss, and proteinuria.

**Table 1: Number and percentage of dogs with adverse reactions in the 28-day placebo-controlled clinical study**

Adverse reactions	PROIN-treated (N=123)	Placebo-treated (N=61)
Emesis	20.3%	8.2%
Hypertension ( $\geq 160$ mmHg) <sup>1</sup>	19.5%	14.7%
Anorexia	16.3%	3.3%
Body weight loss (>5%) <sup>2</sup>	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%

<sup>1</sup>One or more systolic blood pressure readings of  $\geq 160$  mmHg

<sup>2</sup>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.

One-hundred-fifty-seven dogs continued into the 6-month open-label clinical study. The most common adverse reactions are listed in Table 2 below. In addition, one dog exhibited progressively worsening hypertension with proteinuria. Five dogs enrolled in the study with pre-existing heart disease. Of these, one dog developed systolic failure with an unknown relation to treatment.

**Table 2: Number and percentage of dogs with adverse reactions in the 6-month open-label clinical study**

Adverse reactions	Total N=125
Hypertension ( $\geq 160$ mmHg) <sup>1</sup>	34.6%
Body Weight loss ( $\geq 5\%$ )	24.8%
Emesis	19.7%
Proteinuria	15.3%
Anorexia	10.2%
Diarrhea	6.4%
Lethargy	5.7%
Anxiety/behavior change/aggression	5.7%

<sup>1</sup>Percent of dogs with systolic blood pressures of  $\geq 160$  mmHg on day -7 were 30.2% and on day 0 were 33.3%.

## POST APPROVAL EXPERIENCE (2015):

The following adverse events are based on voluntary, post approval reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The signs reported are listed in decreasing order of reporting frequency by body system:

Gastrointestinal: Vomiting, anorexia, diarrhea, hypersalivation,

Behavioral: Agitation, lethargy, vocalization, confusion,

General body system: Polydipsia, weight loss, weakness, fever,

Respiratory: Panting,

Dermatological: Erythema, piloerection,

Hepatic: Elevated serum alanine aminotransferase (ALT), elevated serum alkaline phosphatase (ALP),

Neurologic: Ataxia, seizures, tremors,

Renal/Urinary: Renal failure, hematuria, urinary retention,

Cardiovascular: Tachycardia, hypertension, bradycardia, arrhythmias,

Sensory: Ophthalmic disorders, mydriasis and eye redness.

In some cases, death, including euthanasia, has been reported. Sudden death was sometimes preceded by neurologic signs, vocalization, or collapse. A necropsy of one dog revealed subarachnoidal and intraventricular hemorrhage in the brain.

The following signs have been reported more often with a dose higher than the recommended dosage: agitation, arrhythmia, bradycardia, erythema, fever, hypersalivation, hypertension, lethargy, mydriasis, panting, piloerection, tachycardia, tremor, and urinary retention.

For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Pegasus Laboratories at 1-800-874-9764. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

**Information for Owner or Person Treating Animal:** Always follow the dosage instructions for PROIN provided by your veterinarian. Monitor your dog after giving PROIN to be sure all of it was consumed. If you have difficulty giving PROIN, contact your veterinarian.

It may take several days of treatment with PROIN before urinary incontinence improves. If you miss a dose, give it as soon as you remember. If it is close to the time for the next dose, skip the dose you missed and go back to the regular dosing schedule. Do not give two doses at once. PROIN should only be given to the dog for which it was prescribed. Because PROIN is flavored, store in a secure area.

Dogs may willingly consume more than the recommended dosage of PROIN Chewable Tablets. Instances of dogs chewing through closed bottles of PROIN and eating the bottles contents have been reported. Keep the product in a secured storage area out of the reach of pets in order to prevent accidental ingestion or overdose. Contact your veterinarian immediately if the dog ingests more tablets than prescribed or if other pets ingest PROIN Chewable Tablets. In the case of accidental ingestion by humans, contact a physician immediately.

Contact your veterinarian if you notice restlessness or irritability, loss of appetite, the incontinence persists or worsens, or any other unusual signs.

Consult your veterinarian before using PROIN with any other medications.

**Clinical Pharmacology:** Phenylpropanolamine is a chemical analogue of the endogenous sympathomimetic amines. It is an  $\alpha$ -adrenergic agent which has been reported to increase urethral tone in dogs.<sup>2</sup> Its mechanism of action is not well determined, but it is believed to cause the release of norepinephrine by indirectly stimulating both the  $\alpha$  and  $\beta$ -adrenergic receptors of the smooth muscle to increase smooth muscle tone of the urethra, bladder neck, and the internal urethral sphincter.<sup>3,4</sup>

The pharmacokinetics of phenylpropanolamine in dogs has not been well studied. In humans, phenylpropanolamine is readily absorbed after oral administration of solid dosage forms and has an onset of action of approximately 15-30 minutes and duration of effect of about three hours. In a published study in dogs, phenylpropanolamine disposition was characterized in three dogs administered phenylpropanolamine intravenously and orally in immediate-release and controlled-release formulations.<sup>5</sup> The terminal elimination half-life averaged  $3.5 \pm 0.5$  hours after the intravenous dose. Oral absorption from the immediate-release capsule was rapid and bioavailability was  $98.2 \pm 6.9$  percent. Absorption of phenylpropanolamine from the controlled-release dosage form was biphasic; an initial rapid phase was followed by a second, slower absorption phase which continued over 16 hours. Plasma concentrations then declined with a half-life roughly parallel to the intravenous and oral immediate-release half-lives. Oral bioavailability from the controlled-release tablet was  $93.7 \pm 5.9$  percent.

**Effectiveness:** A 28-day placebo-controlled clinical study was conducted in 21 study sites across the U.S. The study included 184 dogs with urinary incontinence due to sphincter hypotonus of which 127 dogs (100 female, 27 male) were evaluated for effectiveness. Dogs were randomly assigned either to receive 2 mg/kg PROIN (123 dogs) or placebo (61 dogs) administered orally twice daily for 28 days. PROIN was effective in controlling urinary incontinence based on a decrease in urinary accidents per week. Changes to hematology and serum chemistry were not considered clinically significant or related to treatment.

**Table 3: 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

One-hundred fifty seven dogs continued into the 6-month open-label clinical study conducted in 21 study sites across the U.S. All the dogs had participated in the 28-day placebo-controlled clinical study and had urinary incontinence due to sphincter hypotonus. Dogs were administered 2 mg/kg PROIN orally twice daily for 180 days. PROIN was effective for the control of urinary incontinence for 180 days based on 98.1% owner satisfaction. The dogs averaged just over one accident per dog per week. Changes in hematology and serum chemistry were not considered clinically significant or related to treatment.

The dogs voluntarily consumed 53.9% of the doses and 33.7% of the doses in food. The owners pill the dogs 12.1% of the doses and were unable to administer 0.3% of the doses.

**Animal Safety Studies:** In a target animal safety study, PROIN was administered to 32 healthy male and female Beagle dogs at 0, 2, 6 and 10 mg/kg of body weight (0, 1, 3 and 5 times the recommended dose; 8 dogs per group) twice daily for 26 consecutive weeks. The most pronounced finding was a dose-dependent increase in blood pressure. Mean systolic blood pressure was increased in all PPA-treated groups compared to the control, but mean values for all 4 groups were within the normal range. Mean diastolic and mean MAP (mean arterial pressure) were higher in the 3X and 5X groups, and in the 1X males. Dogs in the 3X and 5X groups had more individual systolic, diastolic, and MAP values above the normal range than the control group dogs. A dose-dependent decrease in heart rate was observed in the 3X and 5X dogs. In the 0, 1, 3, and 5X groups, 5%, 34%, 44%, and 40% of the total number of heart rates obtained from electrocardiograms for each group over the course of the study were below the normal range (70-120 beats per minute), with the lowest value being 51 bpm in 4 of the 1X group dogs. One dog in each of the 1X and 5X groups had an elevated heart rate between 150-180 beats per minute on at least 2 of the 13 physical exams. One dog in each of the 1X and 3X groups developed gallop heart sounds after treatment began that were noted in 12 of 13 and 6 of 13 physical exams respectively. Dogs in the PPA-treated groups exhibited anxious/restless behavior more frequently than the control group. One dog each in the 1X and 3X groups were responsible for the majority of the observations. A decline in mean body weight and body condition was observed in females in all 4 groups, including the control. One female in the 1X group lost 33% body weight. Vomiting and loose stool occurred in a dose-related fashion, and most of the vomiting episodes took place within 1 hour of dosing. Mean platelet counts were higher in at least one of the PPA-treated groups, with individual values up to 1.4X the upper limit of normal (ULN) in the 3X and 5X groups. The 3X and 5X groups had higher mean serum ALT values compared to the control. Mean ALT was within the normal range for all 4

groups. There were more dogs with ALT levels above the normal range in the 3 PPA-treated groups compared to the control, but increased values were transient and less than 1.8X ULN. All dogs had ALT values in the normal range at the conclusion of the study.

In a separate tolerance study, 6 healthy female Beagle dogs were administered PROIN at 20 mg/kg body weight (10 times the recommended dose) twice daily for 21 consecutive days. Mean systolic blood pressure was increased in the 10X group compared to the control, but mean values were within the normal range for both groups. Mean diastolic pressures were above the normal range on days 7 and 21 for the 10X group, and day 14 for the control. The 10X dogs had hypertensive mean MAP values on days 7 and 21, whereas the control dog mean MAP values were in the normal range. There was a trend in 10X dogs for lower heart rates following initiation of PPA treatment. Four of 6 dogs in the 10X group had heart rates below the normal range on day 7, whereas none of the control dogs did. The 10X group dogs had increased hematocrit, hemoglobin, RBC counts, urine specific gravity, and water intake consistent with transient, sub-clinical dehydration that occurred shortly after PPA treatment was started. All 6 dogs in the 10X group vomited at least once during the treatment period, whereas only 1 of the control dogs did. Most of the vomiting episodes took place within 1 hour of dosing. Mean platelet counts were also higher in 10X dogs on all 3 exam days; mean values were above the normal range on day 7, with individual values up to 1.5X ULN. The 10X group had a higher mean serum ALT value on day 7 than the control. Mean ALT values for both groups were in the normal range on all 3 exam days, but 2 dogs in the 10X group had ALT values up to 1.4X ULN on day 7; these elevated values were transient, and all dogs had normal ALT values on days 14 and 21.

For either study, there was no evidence of chronic hypertension-induced target organ damage; there were no clinical findings attributable to PPA on the ophthalmic exams, electrocardiogram evaluation, or gross necropsy and histopathology.

**Storage:** Store at controlled room temperature 20-25°C (68-77°F), excursions permitted between 15-40°C (59-104°F)

**How Supplied:** PROIN is scored and contains 25, 50 or 75 mg phenylpropanolamine hydrochloride per tablet. PROIN is packaged in bottles containing 60 or 180 tablets.

NADA #141-324, Approved by FDA.

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#### References:

1. Watson R, et al. Ephedra alkaloids inhibit platelet aggregation. *Blood Coagulation and Fibrinolysis*, 2010, 21: 266-271.
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3. 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.
4. Noel, S., et al. Combined pharmacokinetic and urodynamic study of the effects of oral administration of phenylpropanolamine in female Beagle dogs. *Vet. Journal*, 2010; 184(2): 201-207.
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References

4. Data on file.

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