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

PROIN ER™
(phenylpropanolamine hydrochloride extended-release tablets)

PROIN®
(phenylpropanolamine 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.**

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.

---

**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). Anomalous 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. If a pet ingests more than the recommended dosage of PROIN Chewable Tablets or PROIN ER™ tablets, contact your veterinarian immediately. 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, warnings, and precautions or visit prnpharmacal.com.

---

References

**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 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

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
**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.
- Acceptability was recorded by the pet owners; 11.4% of the doses were consumedwithout food and 70.8% of the doses were accepted with a small amount of food.
- 99% of owners in the study, when asked on Day 28, assessed their dog as “improved” or “stayed the same.”
- 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.

See product insert for additional information, located on next page.
“P is for PROIN, PROIN is for Pee!”

PROIN® *(phenylpropanolamine hydrochloride)*
Chewable Tablets

Available in 60 ct. and 180 ct. bottles

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

In a six-month study, PROIN achieved 98.1% owner satisfaction for the control of urinary incontinence.

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

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

References
**PROIN ER™**
*(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 (PAA) is the nonproprietary designation for benzenemethanol, a-(1-aminoethyl)-hydrochloride, (R*, S*)-, (±). The empirical formula is C9H13NO•HCl and the molecular weight is 187.67. It is a white crystalline compound having a slight aromatic odor. PAA is freely soluble in water and alcohol but is practically insoluble in ether, benzene and chloroform. The chemical structure of phenylpropanolamine hydrochloride is:

![Chemical Structure of Phenylpropanolamine Hydrochloride](image)

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

**DOSEAGE 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**

<table>
<thead>
<tr>
<th>Body weight in pounds</th>
<th>PROIN ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-20</td>
<td>18 mg</td>
</tr>
<tr>
<td>21-40</td>
<td>36 mg</td>
</tr>
<tr>
<td>41-80</td>
<td>74 mg</td>
</tr>
<tr>
<td>81-125*</td>
<td>145 mg</td>
</tr>
</tbody>
</table>

**Body weight should be rounded to the nearest pound.

**Dogs exceeding 125 lbs should receive the appropriate combination of tablets to achieve the recommended dosage.

**Do not split or crush tablets.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Total N=119</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis</td>
<td>39 (32.8%)</td>
</tr>
<tr>
<td>Body weight loss (≥5%)</td>
<td>34 (28.6%)</td>
</tr>
<tr>
<td>Hypertension (≥160 mmHg)</td>
<td>15 (12.6%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (16.8%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>16 (13.4%)</td>
</tr>
<tr>
<td>Tachycardia (≥160 bpm)</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10 (8.4%)</td>
</tr>
<tr>
<td>Urinary Tract infection</td>
<td>10 (8.4%)</td>
</tr>
<tr>
<td>Elevated Alkaline phosphatase and/or Alanine Aminotransferase</td>
<td>7 (6.0%)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>4 (3.3%)</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>3 (2.5%)</td>
</tr>
<tr>
<td>Increased BUN</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Bradycardia (≤60 bpm)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Seizures/twitching</td>
<td>2 (1.7%)</td>
</tr>
</tbody>
</table>

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 141-326):**

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**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Total N=184</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis</td>
<td>20 (10.9%)</td>
</tr>
<tr>
<td>Hypertension (≥160 mmHg)</td>
<td>34.6%</td>
</tr>
<tr>
<td>Body weight loss (≥5%)</td>
<td>24.8%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>15.3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19.7%</td>
</tr>
<tr>
<td>Bradycardia (≤60 bpm)</td>
<td>7.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.4%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5.7%</td>
</tr>
<tr>
<td>Anxiety/aggression/behavior change</td>
<td>8.2%</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>3.2%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1.7%</td>
</tr>
<tr>
<td>Urinary Tract infection</td>
<td>3.2%</td>
</tr>
<tr>
<td>Decreased food intake</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**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/CMR. 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:

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Total N=125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (≥160 mmHg)</td>
<td>34.6%</td>
</tr>
<tr>
<td>Body weight loss (≥5%)</td>
<td>24.8%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>15.3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19.7%</td>
</tr>
<tr>
<td>Bradycardia (≤60 bpm)</td>
<td>7.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.4%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5.7%</td>
</tr>
<tr>
<td>Anxiety/aggression/behavior change</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

*One or more systolic blood pressure readings of ≥160 mmHg.

*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**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Total N=125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (≥160 mmHg)</td>
<td>34.6%</td>
</tr>
<tr>
<td>Body weight loss (≥5%)</td>
<td>24.8%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>15.3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19.7%</td>
</tr>
<tr>
<td>Bradycardia (≤60 bpm)</td>
<td>7.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.4%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5.7%</td>
</tr>
<tr>
<td>Anxiety/aggression/behavior change</td>
<td>8.2%</td>
</tr>
</tbody>
</table>
Gastrointestinal: Emesis, anorexia, diarrhea, hyper salivation
Behavioral: Agitation, lethargy, vocalization, confusion
General body system: Polydipsia, weight loss, weakness, fever
Respiratory: Panting
Dermatologic: 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 subarachnoid and intraventricular hemorrhage in the brain.

The following signs have been reported more often with a dose higher than the recommended dosage: agitation, ataxia, mydriasis, bradycardia, erythema, fever, hyperventilation, 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 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 secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or dosage.

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:
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. Its mechanism of action is not well determined, but it is believed to cause the release of norepinephrine by indirectly stimulating both the postsynaptic and presynaptic receptors of the smooth muscle to increase smooth muscle tone of the urethra, bladder neck, and the internal urethral sphincter.

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 (Cmax), but the area under the concentration time curve to the last quantifiable concentration (AUCLast) was similar in both fed and fasted states. The small decrease in the post-prandial AUCLast appeared to be attributable to the corresponding increase in the terminal elimination rate constant under the fed conditions. The time to Cmax (Tmax) was more variable in the fasted state, ranging from 1.5 to 6 hours compared to 2 to 6 hours for the fed state. The elimination half-life (t1/2) 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 evaluation, or gross necropsy and histopathology.

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, 3 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 rate values 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 decrease 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, with the 1X and 5X groups having the highest incidence of the emesis episodes taking 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 ALV values compared to the control. Mean ALV was within the normal range for all 4 groups. There were more dogs with ALV 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 ALV 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 dogs mean MAP values were within 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 dogs group had increased hemato crit, hematocrit, RBC counts, urine specific gravity, weight loss and 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 ALV value on day 7 than the control. Mean ALV values for both groups were in the normal range on all 3 exam days, but 2 dogs in the 10X group had ALV values up to 1.4X ULN on day 7, these elevated values were transient, and all dogs had normal ALV 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.


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

REFERENCES:

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®
(phenylpropanolamine 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 (phenylpropanolamine hydrochloride) is a sympathomimetic amine closely related to ephedrine. Phenylpropanolamine hydrochloride (PPA) is the nonproprietary designation for benzenemethanol, (C₁₉H₂₃NO • HCl). The empirical formula is C₁₉H₂₃NO • 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:

\[
\text{PROIN} = \text{C}_9\text{H}_{15}\text{NO} \cdot \text{HCl}
\]

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

Dosage and Administration: The total recommended dosage for oral administration is 2 mg/kg (0.01 mg/lb) of body weight twice daily. PROIN is scored and dosage should be calculated in half-tablet increments.


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.1 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

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>PROIN-treated (N=123)</th>
<th>Placebo-treated (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emesis</td>
<td>20.3%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Hypertension (≥ 160 mmHg)²</td>
<td>19.5%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>16.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Body weight loss (&gt;5%)²</td>
<td>16.1%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>13.0%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Anxiety/aggression/behavior change</td>
<td>9.7%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.3%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>6.5%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5.7%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Musculoskeletal Disorder</td>
<td>3.2%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Insomnia/sleep disorder</td>
<td>2.5%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

¹Percent of dogs with systolic blood pressures of ≥ 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
- Respiratory: Panting
- Dermatological: Erythema, piroxicam
- 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, piroxicam, 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-VENTS 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 dicyclomine 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.

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

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Total N=125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (≥ 160 mmHg)¹</td>
<td>34.6%</td>
</tr>
<tr>
<td>Body Weight loss (≥ 5%)</td>
<td>24.8%</td>
</tr>
<tr>
<td>Emesis</td>
<td>19.7%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>15.3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.4%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5.7%</td>
</tr>
<tr>
<td>Anxiety/behavior change/aggression</td>
<td>5.7%</td>
</tr>
</tbody>
</table>
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 α-adrenergic agent which has been reported to increase urethral tone in dogs. 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. 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. The terminal elimination half-life averaged 3.5 ± 0.5 hours after the intravenous dose. Oral absorption from the immediate-release capsule was rapid and bioavailability was 98.2 ± 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 ± 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 hypotonia 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**

<table>
<thead>
<tr>
<th>Week</th>
<th>Mean Urinary Accidents (PROIN-treated, N=144)</th>
<th>Mean Urinary Accidents (Placebo, N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>9.0</td>
<td>7.8</td>
</tr>
<tr>
<td>1</td>
<td>3.9</td>
<td>4.8</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>4.1</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>1.6</td>
<td>2.8</td>
</tr>
</tbody>
</table>

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 hypotonia. 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 picked 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 increase 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, uric acid, 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°F (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.

**References:**


*Manufactured by:* Pegasus Laboratories, Inc.
*An Employee-Owned Company*
*Pensacola, FL 32514, USA*
PRN® Pharmacal, an employee-owned company, has been dedicated to developing specialized therapeutics that address the unmet, underserved and overlooked needs of the veterinary medicine community since 1978. Our commitment: quality solutions - as needed, when needed.

To learn more about PRN Pharmacal products, visit PRNPharmacal.com or call 1-800-874-9764.