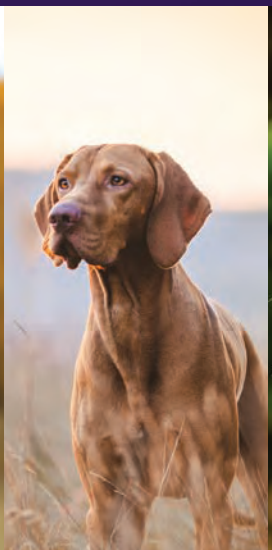
PRN®
PHARMACAL

2025 PRODUCT CATALOG

JANUARY EDITION

In 1978, four men, fueled by the belief that the veterinary community needed a company to service their unmet needs, each put in $5,000, their industry-specific expertise and a huge dose of optimism to found such a company. This company's business would be dedicated to leading the industry in research and development of niche products and drug therapies that address overlooked areas of pet and animal health.

Pro Re Nata is a Latin phrase meaning as the circumstance arises. It has come to be used in prescription medicine as p.r.n. or ***as needed***. This is how PRN® Pharmacal began and it is how we continue to view ourselves today. As true as it was in 1978, the veterinary community can be assured that PRN Pharmacal will be here when needed to provide products that improve animal health and quality of life.

Under the **highest quality and rigor of Current Good Manufacturing Practices (CGMP) and standards**, we strive to provide a wide range of products for the enhancement of animal health in areas of veterinary medicine that are largely under-served. Our mission is to continually improve our products and services to meet the needs of the veterinary industry and is driven by both our **employee-ownership** and a fundamental set of values.

Quality comes first.
To achieve customer satisfaction, the quality of our products and services must be our number one priority.

Continuous improvement.
Knowing that it is essential to our success, we must strive for excellence in everything we do: in our products, in their safety and value – and in our competitiveness.

Our veterinary industry customers are our partners.
Whether that be veterinarians, distributors, dealers or suppliers, the company must maintain mutually beneficial relationships with those partners and our business associates.

Our dedication to animal health goes beyond mission statements and company mottos. We are constantly seeking new, unique products, as well as improvements on formulations, packaging, palatability and ease of use. We know that to grow, we have to meet the needs of companion animals and livestock, the veterinarians who treat them and the owners who rely on animals for their livelihood and companionship. It has been that way from our beginning and will continue that way into our future…

PRN® PHARMACAL

AS NEEDED, WHEN NEEDED

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THIS USED TO WORK GREAT

Until something more advanced came along ...

Upgrade your canine UI treatment to today's technology

PROIN ER™ Approved by FDA under NADA #141-517

Consistent

The patented extended-release technology in PROIN ER™ decreases fluctuation in blood levels throughout the day.

Trusted

As the only once-a-day FDA-approved medication for canine UI due to urethral sphincter hypotonus in dogs, PROIN ER™ is proven safe and effective when used according to approved labeling.

Once-Daily Dosing

Helps improve client compliance, which can improve patient outcomes. Administration timing can be adjusted to maximize effectiveness based on patient's sleep schedule.

Preferred

A recent consumer survey revealed that 97% of dog owners prefer the once-daily dosing of PROIN ER™.*

Easy-to-prescribe weight-band dosing

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

The recommended dosage is 2 to 4 mg/kg (0.9 to 1.8 mg/lb.) of body weight once daily. Once the 24-hour dose is determined, a single PROIN ER™ tablet matching that dose is given one time a day. Administer PROIN ER™ with food. Do not split or crush tablets.

For Important Safety Information, please see the next page.

*Consumer Dog Owner survey conducted by PRN Pharmacal, December 2022.

Learn more at proin-er.com

PROIN ER™

(phenylpropanolamine hydrochloride extended-release tablets)

DESCRIPTION Indicated for the control of urinary incontinence due to urethral sphincter hypotonus in dogs, with the same proven efficacy as PROIN® *(phenylpropanolamine hydrochloride)*, the patented extended-release technology provides a controlled release mechanism for achieving steady absorption and once-a-day dosing.

ITEM #	PRODUCT NAME	SUPPLIED
30034457	PROIN ER™ 18 mg Tablets	30 ct. bottle
30034444	PROIN ER™ 18 mg Tablets	90 ct. bottle
30034557	PROIN ER™ 38 mg Tablets	30 ct. bottle
30034544	PROIN ER™ 38 mg Tablets	90 ct. bottle
30034657	PROIN ER™ 74 mg Tablets	30 ct. bottle
30034644	PROIN ER™ 74 mg Tablets	90 ct. bottle
30034757	PROIN ER™ 145 mg Tablets	30 ct. bottle
30034744	PROIN ER™ 145 mg Tablets	90 ct. bottle

IMPORTANT SAFETY INFORMATION: 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 ER™ tablets. Contact your veterinarian immediately if the dog ingests more tablets than prescribed or if other pets ingest PROIN ER™ tablets.

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 effectiveness and safety of interchangeable use has not been evaluated.

The safe use of 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.

VISIT PROIN-ER.COM FOR PET OWNER RESOURCES AND EDUCATIONAL CONTENT

PHARMACEUTICALS

PROIN®

(phenylpropanolamine hydrochloride)

DESCRIPTION FDA-approved for the control of urinary incontinence due to urethral sphincter hypotonus in dogs. Proprietary flavored tablets are scored for precise dosing.

ITEM #	PRODUCT NAME	SUPPLIED
30031748	PROIN® 25 mg Chewable Tablets	60 ct. bottle
30031750	PROIN® 25 mg Chewable Tablets	180 ct. bottle
30030748	PROIN® 50 mg Chewable Tablets	60 ct. bottle
30030750	PROIN® 50 mg Chewable Tablets	180 ct. bottle
30031548	PROIN® 75 mg Chewable Tablets	60 ct. bottle
30031550	PROIN® 75 mg Chewable Tablets	180 ct. bottle

IMPORTANT SAFETY INFORMATION: 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. Contact your veterinarian immediately if the dog ingests more tablets than prescribed or if other pets ingest PROIN® Chewable Tablets.

PROIN® 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.

The safe use of PROIN® 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.

KBroVet®-CA1

(potassium bromide chewable tablets)

DESCRIPTION French-vanilla flavored tablets indicated for the control of seizures associated with idiopathic epilepsy in dogs. Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-544.

ITEM #	PRODUCT NAME	SUPPLIED
30039748	KBroVet®-CA1 250 mg Chewable Tablets	60 ct. bottle
30039750	KBroVet®-CA1 250 mg Chewable Tablets	180 ct. bottle
30039848	KBroVet®-CA1 500 mg Chewable Tablets	60 ct. bottle
30039850	KBroVet®-CA1 500 mg Chewable Tablets	180 ct. bottle

IMPORTANT SAFETY INFORMATION: Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-544. The most commonly reported side effects were increased appetite and thirst, increased urination, weight gain, sedation, and ataxia. Reversible neurologic signs (sedation, ataxia, weakness) were generally associated with adjunctive potassium bromide treatment or high serum bromide concentrations.

Animals with kidney disease may be predisposed to bromide toxicities. Use caution when changing diets, administering chloride-containing IV fluids, and administering concurrent medications. Careful monitoring is important in dogs that have a condition that may cause difficulty maintaining electrolyte balance.

The safe use of KBroVet®-CA1 has not been evaluated in dogs that are intended for breeding, are pregnant or lactating, or less than 6 months of age.

VISIT KBROVET.COM FOR PET OWNER RESOURCES AND EDUCATIONAL CONTENT

PRN® PHARMACAL

PHARMACEUTICALS

Reconcile®

(fluoxetine hydrochloride)

DESCRIPTION Indicated for the treatment of canine separation anxiety in conjunction with a behavior modification plan. Flavored chewable tablets for ease of dosing and pet acceptance.

ITEM #	PRODUCT NAME	SUPPLIED
10034057	Reconcile® 8 mg Chewable Tablets	30 ct. bottle
10036844	Reconcile® 8 mg Chewable Tablets	90 ct. bottle
10034157	Reconcile® 16 mg Chewable Tablets	30 ct. bottle
10036944	Reconcile® 16 mg Chewable Tablets	90 ct. bottle
10034257	Reconcile® 32 mg Chewable Tablets	30 ct. bottle
10037044	Reconcile® 32 mg Chewable Tablets	90 ct. bottle
10034357	Reconcile® 64 mg Chewable Tablets	30 ct. bottle
10037144	Reconcile® 64 mg Chewable Tablets	90 ct. bottle

IMPORTANT SAFETY INFORMATION: The most common adverse events reported in decreasing order of reported frequency are: decreased appetite, depression/lethargy, shaking/shivering/tremor, vomiting, restlessness and anxiety, seizures, aggression, diarrhea, mydriasis, vocalization, weight loss, panting, confusion, incoordination, and hypersalivation. Reconcile chewable tablets are contraindicated for dogs with a history of seizures or when used with MAOIs. For product label, including complete safety information, see package insert.

VISIT RECONCILE.COM FOR PET OWNER RESOURCES AND EDUCATIONAL CONTENT

ReBalance®

Antiprotozoal Oral Suspension

(sulfadiazine and pyrimethamine)

DESCRIPTION Antiprotozoal oral suspension, when administered under labeled conditions, is an FDA-approved, safe and effective treatment for horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

ITEM #	PRODUCT NAME	SUPPLIED
30024711	ReBalance® Antiprotozoal Oral Suspension	1 qt. bottle

IMPORTANT SAFETY INFORMATION: Prior to treatment with ReBalance® Antiprotozoal Oral Suspension, EPM should be distinguished from other diseases that may cause ataxia in horses. Injuries or lameness may also complicate the evaluation of an animal with EPM. In most instances, ataxia due to EPM is asymmetrical and affects the front and/or the hind limbs.

Treatment may cause generalized bone marrow suppression, anemia, leukopenia, neutropenia and thrombocytopenia. A complete blood count (CBC) should be performed monthly to monitor horses for development of these conditions. The administration of the drug may need to be discontinued and/or treatments for bone marrow suppression initiated.

Other, less frequent side effects included decreased appetite, loose stools, and mild colic. In most cases, the gastrointestinal signs were self-limiting and did not require discontinuation of treatment.

Worsened neurologic deficits (treatment crisis) may be observed during a period beginning with the first few days of treatment with ReBalance and ranging out to 5 weeks. This neurologic deficit exacerbation may be the result of an inflammatory reaction to the dying parasites in the CNS tissue.

The safe use of ReBalance® Antiprotozoal Oral Suspension in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. The safety of ReBalance® with concomitant therapies in horses has not been evaluated.

ReBalance® is not for use in horses with known hypersensitivity to sulfonamide drugs or pyrimethamine. Refer to the prescribing information for complete details.

With the Sē•Qual™ product line of generic drugs from PRN Pharmacal, veterinarians can now rely on brand-name quality and service in a much more cost-effective way. Confidently stock your clinic and provide your clients with the pharmaceuticals they need and trust.

Firocoxib Chewable Tablets for Dogs

a Sē•Qual™ product

DESCRIPTION FDA-approved Firocoxib Chewable Tablets for Dogs are administered for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain and inflammation associated with soft-tissue and orthopedic surgery in dogs.

ITEM #	PRODUCT NAME	SUPPLIED
30035648	Firocoxib Chewable Tablets for Dogs 57 mg	60 ct. bottle
30035748	Firocoxib Chewable Tablets for Dogs 227 mg	60 ct. bottle

IMPORTANT SAFETY INFORMATION: As a class, cyclooxygenase inhibitory NSAIDs like Firocoxib Chewable Tablets for Dogs may be associated with gastrointestinal, kidney or liver side effects. Dogs should be evaluated for pre-existing conditions, and currently prescribed medications, prior to treatment with Firocoxib Chewable Tablets for Dogs, then monitored while on therapy. Concurrent use with another NSAID, corticosteroids or nephrotoxic medication should be avoided or monitored closely. For more information, please see full prescribing information.

Firocoxib Tablets for Horses

a Sē•Qual™ product

DESCRIPTION FDA-approved Firocoxib Tablets for Horses are indicated for the control of pain and inflammation associated with osteoarthritis (OA) in horses. It is a generic form of the first and only COXIB class NSAID for horses.

ITEM #	PRODUCT NAME	SUPPLIED
30039048	Firocoxib Tablets for Horses 57 mg	60 ct. bottle

IMPORTANT SAFETY INFORMATION: As with any prescription medication, prior to use, a veterinarian should perform a physical examination and review the horse's medical history. A veterinarian should advise horse owners to observe for signs of potential drug toxicity. As a class, nonsteroidal anti-inflammatory drugs may be associated with gastrointestinal, hepatic and renal toxicity. Use withother NSAIDs, corticosteroids or nephrotic medication should be avoided. Firocoxib Tablets for Horses has not been tested in horses less than 1 year of age or in breeding horses, or pregnant or lactating mares.

Vetadryl®

(diphenhydramine HCl)

DESCRIPTION Diphenhydramine HCl has been used as an aid in the management of allergies, insect bites, motion sickness, travel anxiety, and other conditions. Scored, proprietary chicken-liver flavored tablets.

ITEM #	PRODUCT NAME	SUPPLIED
30032945	Vetadryl® 10 mg Flavored Tablets	250 ct. bottle
30033045	Vetadryl® 30 mg Flavored Tablets	250 ct. bottle

IMPORTANT SAFETY INFORMATION: A diphenhydramine HCl overdose can cause CNS stimulation (lethargy, somnolence), anti-cholinergic effects (dry mouth, urinary retention), and GI effects (diarrhea, vomiting, anorexia). This products may cause paradoxical excitement in cats. Contact your veterinarian if your animal experiences any of the above conditions after taking this product. The safety of this product in pregnant, breeding and lactating animals is unknown. Do not use this product in breeding animals.

Duralactin® Canine Chewable Tablets

Joint Health Supplement for Dogs

DESCRIPTION Vanilla-flavored tablets contain Microlactin®, an exclusive dried milk protein concentrate derived from hyperimmunized cows for long-term management of inflammatory conditions in dogs and puppies. Duralactin® products also support normal activity and wellness.*

ITEM #	PRODUCT NAME	SUPPLIED
3002932	Duralactin® Canine Chewable Tablets	60 ct. bottle
3004948	Duralactin® Canine Chewable Tablets	180 ct. bottle

Duralactin® Canine Soft Chews

Joint Health Supplement for Dogs

DESCRIPTION Sweetened, chicken-liver flavored soft chews contain Microlactin®, an exclusive dried milk protein concentrate derived from hyperimmunized cows for long-term management of inflammatory conditions in dogs and puppies. Joint Plus Soft Chews also contain Glucosamine, HCl and MSM to support joint health and function. Duralactin® products also support normal activity and wellness.*

ITEM #	PRODUCT NAME	SUPPLIED
100521847	Duralactin® Canine Soft Chews	60 ct. bottle
100521848	Duralactin® Canine Soft Chews	90 ct. bottle
100522704	Duralactin® Canine Joint Plus Soft Chews	60 ct. bottle
100522703	Duralactin® Canine Joint Plus Soft Chews	90 ct. bottle

*THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT ANY DISEASE.

Duralactin® Feline Capsules

Joint Health Supplement for Cats

DESCRIPTION Gelatin capsule contains Microlactin®, an exclusive dried milk protein concentrate derived from hyperimmunized cows for use in cats and kittens to help manage inflammatory conditions. Duralactin® products also support normal activity and wellness. Capsules can be opened, and the powdered product can be mixed with food.*

ITEM #	PRODUCT NAME	SUPPLIED
3003829	Duralactin® Feline Capsules	60 ct. bottle

Duralactin® Feline L-Lysine Paste

Joint, Respiratory and Ocular Health Supplement for Cats

DESCRIPTION In an easy-to-use, dial-dose syringe, this natural chicken-flavor paste contains Microlactin®, an exclusive dried milk protein concentrate derived from hyperimmunized cows for use in cats and kittens to help manage inflammatory conditions. Includes L-Lysine to help support respiratory and ocular health. Duralactin® products also support normal activity and wellness.*

ITEM #	PRODUCT NAME	SUPPLIED
100504080	Duralactin® Feline L-Lysine Paste	32.5 mL syringe

VISIT DURALACTIN.COM FOR PET OWNER RESOURCES AND EDUCATIONAL CONTENT

Duralactin® Feline + Fatty Acids Soft Chews

Joint Health Supplement for Cats

DESCRIPTION Sweetened, chicken-liver flavored soft chews contain Microlactin®, an exclusive dried milk protein concentrate derived from hyperimmunized cows for use in cats and kittens to help manage inflammatory conditions. Includes Omega-3 and Omega-6 Fatty Acids to help manage the production of inflammatory substances. Duralactin® products also support normal activity and wellness.*

ITEM #	PRODUCT NAME	SUPPLIED
100521850	Duralactin® Feline + Fatty Acids Soft Chews	60 ct. bottle

Duralactin® Equine Pellets

Joint Health Supplement for Horses

DESCRIPTION Easy-to-feed pellets contain Microlactin®, an exclusive dried milk protein concentrate derived from hyperimmunized cows for the management of inflammatory conditions in horses. Equine Joint Plus Pellets also contain Glucosamine HCl, Chondroitin, and Vitamin C to support joint health and function. Duralactin® products also support normal activity and wellness.*

ITEM #	PRODUCT NAME	SUPPLIED
100523768	Duralactin® Equine Pellets	1.875 lb. bag
100523767	Duralactin® Equine Joint Plus Pellets	3.75 lb. bag

CitraVet®

Potassium Citrate Supplement

DESCRIPTION A double-scored chewable tablet for dogs and cats containing potassium citrate that may be given as part of a maintenance program for pets that require urine pH management. Proprietary chicken-liver flavored.*

ITEM #	PRODUCT NAME	SUPPLIED
30032848	CitraVet®	60 ct. bottle

CranMate®

Cranberry Supplement

DESCRIPTION With a patented extraction process that eliminates unwanted sugar, and made with American Cranberry extract rich in Type-A proanthocyanidins (PACs) and antioxidants, these scored tablets are formulated specifically to support the urinary tract health of dogs and cats.*

ITEM #	PRODUCT NAME	SUPPLIED
30032648	CranMate®	60 ct. bottle

*THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT ANY DISEASE.

CoproBan®

Coprophagia Deterrent

DESCRIPTION A convenient, easy-to-use, roast beef flavored chew formulated with MSG and cellulose to assist in the breakdown of fiber, rendering the taste and texture of the stool unpleasant to eat. CoproBan® may be fed to cats to discourage dogs from raiding the litter box.*

ITEM #	PRODUCT NAME	SUPPLIED
30032562	CoproBan®	40 ct. bottle

VISIT STOPPOOPEATING.COM FOR PET OWNER RESOURCES AND EDUCATIONAL CONTENT

*THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT ANY DISEASE.

Calsorb™

Calcium Nutritional Supplement

DESCRIPTION Gel-based nutritional supplement supplied in a simple-to-administer, clear dosing syringe that provides an oral alternative to maintain healthy calcium levels when an IV is not desireable or feasible.*

ITEM #	PRODUCT NAME	SUPPLIED
30010835	Calsorb™	12 mL syringe

OPTIMA 365™

Essential Fatty Acids Nutritional Supplement

DESCRIPTION With a combination of fatty acids, amino acids, vitamins and minerals, this flavored (chicken/fish combination) dietary addition provides a low-calorie liquid supplement that supports overall pet health. With no artificial colors or flavors and a 1:1 ratio of Omega-6 to Omega-3 Essential Fatty Acids, the formulation of ingredients promotes a healthy skin and coat, as well as the reduction of non-seasonal shedding.*

ITEM #	PRODUCT NAME	SUPPLIED
3005441	OPTIMA 365™	16 oz. bottle
3005443	OPTIMA 365™	1 gal. bottle

Liqui-Tinic™ 4X

Iron/Vitamin Nutritional Supplement

DESCRIPTION Liquid, liver-flavored nutritional supplement for oral use in livestock and companion animals that supplies iron and B-complex vitamins in support of overall health and well-being.*

ITEM #	PRODUCT NAME	SUPPLIED
30022003	Liqui-Tinic™ 4X	2 oz. bottle
30022022	Liqui-Tinic™ 4X	1 gal. bottle

STAT®

High Calorie Nutritional Supplement

DESCRIPTION At 185 calories per ounce, this vanilla-flavored high-calorie liquid provides additional nutrition to animals that may be under stress. Either administrated "as is" to animals with decreased appetite or top-dressed over the animal's normal diet, the product will help maintain nutrient balances in convalescing, underweight, lactating and working animals for their overall health.*

ITEM #	PRODUCT NAME	SUPPLIED
30022409	STAT®	16 oz. bottle

*THESE STATEMENTS HAVE NOT BEEN EVALUATED BY THE FOOD AND DRUG ADMINISTRATION. THIS PRODUCT IS NOT INTENDED TO DIAGNOSE, TREAT, CURE OR PREVENT ANY DISEASE.

CMPK Bolus & Drench

Livestock Mineral/ Vitamin Supplement

DESCRIPTION Either in specially formulated slow release bolus or as a liquid drench, this supplement includes all major macrominerals required for overall wellness of healthy livestock that may have nutritional deficiencies or may benefit from meeting additional dietary needs.

ITEM #	PRODUCT NAME	SUPPLIED
30000547	CMPK Slow Release Bolus	50 ct. jar
30020122	CMPK Drench Plus™	1 gal. bottle

High Potency Calcium Gel®

Calcium Livestock Supplement

DESCRIPTION A nutritional supplement gel formulated to be quickly absorbed comes in an easy-to-use tube for administration before and after calving or during times when livestock may need additional calcium.

ITEM #	PRODUCT NAME	SUPPLIED
30010936	High Potency Calcium Gel®	300 mL tube

Hi-Energy Supplement®

High Calorie Livestock Supplement

DESCRIPTION Formulated with amino acids, B-complex vitamins, poultry liver, iron and propylene glycol, this oral gel in an easy-to-administer tube can provide additional calories to meet heightened nutritional needs.

ITEM #	PRODUCT NAME	SUPPLIED
30010236	Hi-Energy Supplement®	300 mL tube

Magna Gel™

Magnesium Livestock Supplement

DESCRIPTION Intended for beef and dairy cattle, this gel in an easy-to-administer tube acts as a nutritional supplement to supply additional magnesium and calcium for those animals in need.

ITEM #	PRODUCT NAME	SUPPLIED
30010336	Magna Gel™	300 mL tube

Endosorb®

Anti-Diarrheal Supplement

DESCRIPTION A low-cost treatment that supports intestinal function, Endosorb® products are formulated to stabilize stool consistency and soothe the gastrointestinal tract. Formulated with a proven attapulgite to help animals that may require improvement of stool viscosity.

ITEM #	PRODUCT NAME	SUPPLIED
30001347	Endosorb® Bolus	50 ct. jar
30030251	Endosorb® Tablets	500 ct. bottle
30021704	Endosorb® Suspension	4 oz. bottle
30021722	Endosorb® Suspension	1 gal. bottle

⚠ **PROP 65:** This product in bolus and tablet presentations can expose users to crystalline silica, which when airborne particles of respirable size are inhaled is known to the State of California to cause cancer. For more information got to www.P65Warnings.gov.

GastroMate®

Digestive Health Supplement

DESCRIPTION A direct-fed microbial probiotic gel that contains billions of live (viable) naturally occurring microorganisms, pasteurized spray dried egg product, vitamins, and antioxidants. Includes easily digestible protein and soluble, dietary fiber, as well as naturally occurring sweetened salmon/pork flavoring for easier acceptance by dogs.

ITEM #	PRODUCT NAME	SUPPLIED
30012538	GastroMate® Canine IgY Plus Gel	15 mL syringe

PRN® PHARMACAL

GASTROINTESTINAL SUPPORT

Pet-Ema®

Single Use Enema

DESCRIPTION Disposable single use enema for dogs and cats. Aids in maintaining healthy lower bowel function. Includes stool softener and laxative.

ITEM #	PRODUCT NAME	SUPPLIED
30022835	Pet-Ema®	12 mL syringe
30021934	Feline Pet-Ema™	6 mL syringe

ProZyme®

Enzyme Replacement Supplement

DESCRIPTION Unlike most enzyme supplements for pets, ProZyme® is an all-natural combination of plant-origin enzymes (including cellulase) in an odorless, palatable powder that can be mixed in with a pet's food to provide improved digestive health resulting in overall nutritional benefits.

ITEM #	PRODUCT NAME	SUPPLIED
30042384	ProZyme® Powder 85 g	3 oz. bottle
30042385	ProZyme® Powder 200 g	7 oz. bottle
30042386	ProZyme® Powder 454 g	1 lb. bottle

Vet-Kem® Yard Spray

permethrin

DESCRIPTION Home yard spray that kills mosquitoes, fleas, ticks, ants and over 40 other insects, including Deer ticks which may carry Lyme disease. For monthly control, product easily attaches to garden hose to treat up to 5,000 square feet of lawns, trees, shrubs, roses and other flowers.

ITEM #	PRODUCT NAME	SUPPLIED
100527195	Vet-Kem® Yard Spray	32 oz. hose-end sprayer

Vet-Kem® Fogger

(S)-methoprene/permethrin

DESCRIPTION Prevents flea reinfestation and flea build-up for up to seven months. Comes with three-pack of foggers with each 3-ounce can able to treat up to 3,000 cubic feet. Indoor fogger leaves no lingering odor or stains. Kills fleas and their hatching eggs, ticks, cockroaches, ants, spiders, mosquitoes and silverfish.

ITEM #	PRODUCT NAME	SUPPLIED
100526871	Vet-Kem® Fogger	3 x 3 oz. cans

Vet-Kem® Carpet and Premise Spray

(S)-methoprene/permethrin/ phenothrin/piperonyl butoxide/ MGK 264

DESCRIPTION Help keep homes flea-free for up to seven months from a single treatment with an easy-to-use aerosol spray for use as a spot treatment on carpets, rugs, upholstery, drapes and other places where fleas may hide. Specifically designed for in-home usage with an odor-free, stain-free and no sticky-mess formulation. Delivers 100% knock down of adult fleas in ten minutes. Prevents reinfestation and flea build-up for 7 months. Treats up to 2,000 square feet.

ITEM #	PRODUCT NAME	SUPPLIED
100526870	Vet-Kem® Carpet and Premise Spray	16 oz. can

Vet-Kem® Home Spray

(S)-methoprene/etofenprox/piperonyl butoxide

DESCRIPTION Home pump spray that kills fleas, ticks, cockroaches, ants, spiders, flies, mosquitoes, bed bugs and other listed insects. Dual action kills and prevents new infestations. Formulated to stop hatching eggs from developing into adult fleas and kills pre-adult fleas (larvae) before they grow up to bite for up to seven months. Targeted spray pattern provides good coverage of hard-to-reach cracks and crevices in apartments, homes, garages, bedrooms and attics. Can be used directly on bugs and in places where they hide and breed. Kills pests and helps keep them from coming back.

ITEM #	PRODUCT NAME	SUPPLIED
100527067	Vet-Kem® Home Spray	24 oz. bottle

Vet-Kem® Flea, Tick & Bot Spray

(S)-methoprene/pyrethrins/ piperonyl butoxide/MGK 264

DESCRIPTION Quick-acting on-animal spray that kills and repels fleas, ticks (including those that may carry Lyme disease) lice, flies, mosquitoes and gnats. Also, kills flea eggs and prevents bot fly eggs from hatching. Easy-to-apply pump spray for dogs, cats and horses, provides killing and repellency from common pests that your animal companions may encounter. Provides two months of protection. May be used on puppies and kittens above 3 lb. and over 12 weeks of age.

ITEM #	PRODUCT NAME	SUPPLIED
100527066	Vet-Kem® Flea, Tick & Bot Spray	16 oz. bottle

Vet-Kem® Flea and Tick Shampoo for Dogs & Cats

(S)-methoprene/pyrethrins/ piperonyl butoxide

DESCRIPTION Pearlescent shampoo that kills fleas, ticks and lice on contact, as well as, prevents new flea eggs from hatching for 28 days for dogs, puppies, cats and kittens. Sensitive skin formula is a concentrated lathering shampoo enriched with aloe, lanolin, and oatmeal to leave the coat soft, shining and manageable. The shampoo removes loose dandruff, dirt, and scales. May be used on puppies and kittens over 12 weeks of age.

ITEM #	PRODUCT NAME	SUPPLIED
100527065	Vet-Kem® Flea and Tick Shampoo for Dogs & Cats	12 oz. bottle
100531084	Vet-Kem® Flea and Tick Shampoo for Dogs & Cats	1 gal. bottle

Mycodex® Plus Environmental Control™ Aerosol Household Spray

linalool/pyriproxyfen/permethrin/MGK 264

DESCRIPTION Aerosol spray with a botanically derived insecticide (linalool) that kills all four stages of the flea: adults, eggs, pupae and larvae to break the fleas life cycle and control reinfestation for up to 210 days. Also kills ticks, roaches, ants, spiders, lice, crickets, centipedes, waterbugs, silverfish and sowbugs.

ITEM #	PRODUCT NAME	SUPPLIED
100530868	Mycodex® Plus Environmental Control™ Aerosol Household Spray	16 oz. can

Mycodex® All-In-One® Flea & Tick Spray

(S)-methoprene/pyrethrins/ piperonyl butoxide/MGK 264

DESCRIPTION Specially designed for dogs, cats, puppies, and kittens 12 weeks of age and older, a fast-acting formulation that kills and repels lice, flies, mosquitos, gnats, fleas, and ticks, including those that carry Lyme disease. Works for up to 2 months.

ITEM #	PRODUCT NAME	SUPPLIED
100531070	Mycodex® All-In-One® Flea & Tick Spray	16 oz. bottle

Mycodex® Flea & Tick Shampoo P³

pyrethrins/piperonyl butoxide

DESCRIPTION Favored by professional groomers across the country, Mycodex® Flea & Tick Shampoo P³ is a concentrated lathering shampoo enriched with coconut extract, lanolin, and aloe. Leaves coat soft and shining. The shampoo removes loose dandruff, dirt and scales, while killing labeled pests that may be causing discomfort.

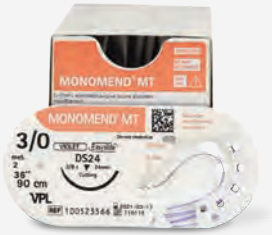
ITEM #	PRODUCT NAME	SUPPLIED
100531072	Mycodex® Flea & Tick Shampoo P³	6 oz. bottle
100531057	Mycodex® Flea & Tick Shampoo P³	12 oz. bottle
100531058	Mycodex® Flea & Tick Shampoo P³	1 gal. bottle

Monomend® ST

Monofilament Short-Term Absorbable Suture

DESCRIPTION An undyed, monofilament short-term, synthetic absorbable suture providing 6-7 days of wound support with complete absorption in 56 days (0% tensile strength between 14-21 days). Absorbable synthetic suture comprised of a terpolymer of glycolide, trimethylene carbonate and caprolactone.

ITEM #	PRODUCT NAME	SUPPLIED
100523604	Monomend® ST RST-VR490-1 (5-0) DSMP11 (3/8 RC) 18″	12 x 1 box
100523605	Monomend® ST RST-VR463-1 (5-0) DSMP13 (3/8 RC) 18″	12 x 1 box
100523606	Monomend® ST RST-VR494-1 (4-0) DSMP13 (3/8 RC) 18″	12 x 1 box
100523607	Monomend® ST RST-VR497-1 (3-0) DSMP19 (3/8 RC) 18″	12 x 1 box
100523608	Monomend® ST RST-VR214-1 (4-0) HR17 (1/2 TP) 18″	12 x 1 box



Monomend® MT

Monofilament Mid-Term Absorbable Suture

DESCRIPTION A violet, monofilament mid-term, synthetic absorbable suture providing 14 days of wound support with complete absorption in 60-90 days (0% initial tensile strength after 28 days). Absorbable synthetic suture comprised of a terpolymer of glycolide, caprolactone and trimethylene.

ITEM #	PRODUCT NAME	SUPPLIED
100523545	Monomend® MT RM-Y463-1 (5-0) DSMP13 (3/8 RC) 18″	12 x 1 box
100523562	Monomend® MT RM-Y464-1 (4-0) DSMP13 (3/8 RC) 18″	12 x 1 box
100523563	Monomend® MT RM-Y844-1 (5-0) DSMP16 (3/8 RC) 18″	12 x 1 box
100523564	Monomend® MT RM-Y922-1 (4-0) DS19 (3/8 RC) 36″	12 x 1 box
100523565	Monomend® MT RM-Y923-1 (3-0) DS19 (3/8 RC) 36″	12 x 1 box
100523566	Monomend® MT RM-Y942-1 (3-0) DS24 (3/8 RC) 36″	12 x 1 box
100523567	Monomend® MT RM-Y943-1 (2-0) DS24 (3/8 RC) 36″	12 x 1 box
100523568	Monomend® MT RM-Y987-1 (0) DS30 (3/8 RC) 36″	12 x 1 box
100523569	Monomend® MT RM-Y966-1 (2-0) HS37s (1/2 RC) 36″	12 x 1 box
100523570	Monomend® MT RM-Y967-1 (0) HS37s (1/2 RC) 36″	12 x 1 box
100523571	Monomend® MT RM-Y968-1 (1) HS37s (1/2 RC) 36″	12 x 1 box
100523572	Monomend® MT RM-Y303-1 (5-0) HR17 (1/2 TP) 18″	12 x 1 box
100523573	Monomend® MT RM-Y304-1 (4-0) HR17 (1/2 TP) 36″	12 x 1 box
100523574	Monomend® MT RM-Y315-1 (4-0) HR26 (1/2 TP) 36″	12 x 1 box
100523575	Monomend® MT RM-Y316-1 (3-0) HR26 (1/2 TP) 36″	12 x 1 box
100523576	Monomend® MT RM-Y317-1 (2-0) HR26 (1/2 TP) 36″	12 x 1 box
100523577	Monomend® MT RM-Y761-1 (3-0) HR26s (1/2 TP) 36″	12 x 1 box
100523578	Monomend® MT RM-Y762-1 (2-0) HR26s (1/2 TP) 36″	12 x 1 box
100523579	Monomend® MT RM-Y344-1 (3-0) HR37s (1/2 TP) 36″	12 x 1 box
100523580	Monomend® MT RM-Y345-1 (2-0) HR37s (1/2 TP) 36″	12 x 1 box
100523581	Monomend® MT RM-Y346-1 (0) HR37s (1/2 TP) 36″	12 x 1 box
100523582	Monomend® MT RM-Y347-1 (1) HR37s (1/2 TP) 36″	12 x 1 box

Monomend® MaX

Monofilament Long-Term Absorbable Suture

DESCRIPTION A violet, monofilament long-term, synthetic absorbable suture ideal for cases where extended wound support of more than 4 weeks is desired providing wound support for 35 days with complete absorption in 180-210 days (0% tensile strength at 70 days). Absorbable synthetic suture comprised of a polydioxanone.

ITEM #	PRODUCT NAME	SUPPLIED
100523583	Monomend® MaX RX-Z421-1 (5-0) DS19 (3/8 RC) 27″	12 x 1 box
100523584	Monomend® MaX RX-Z397-1 (4-0) DS19 (3/8 RC) 27″	12 x 1 box
100523585	Monomend® MaX RX-Z398-1 (3-0) DS19 (3/8 RC) 27″	12 x 1 box
100523586	Monomend® MaX RX-Z452-1 (3-0) DS24 (3/8 RC) 27″	12 x 1 box
100523587	Monomend® MaX RX-Z451-1 (2-0) DS24 (3/8 RC) 27″	12 x 1 box
100523588	Monomend® MaX RX-Z969-1 (2-0) HS26s (1/2 RC) 27″	12 x 1 box
100523589	Monomend® MaX RX-Z970-1 (0) HS26s (1/2 RC) 27″	12 x 1 box
100523590	Monomend® MaX RX-Z466-1 (2-0) HS37s (1/2 RC) 27″	12 x 1 box
100523591	Monomend® MaX RX-Z467-1 (0) HS37s (1/2 RC) 27″	12 x 1 box
100523592	Monomend® MaX RX-Z310-1 (4-0) HR22 (1/2 TP) 27″	12 x 1 box
100523593	Monomend® MaX RX-Z311-1 (3-0) HR22 (1/2 TP) 27″	12 x 1 box
100523594	Monomend® MaX RX-Z315-1 (4-0) HR26 (1/2 TP) 27″	12 x 1 box
100523595	Monomend® MaX RX-Z316-1 (3-0) HR26 (1/2 TP) 27″	12 x 1 box
100523596	Monomend® MaX RX-Z317-1 (2-0) HR26 (1/2 TP) 27″	12 x 1 box
100523597	Monomend® MaX RX-Z332-1 (3-0) HR26s (1/2 TP) 27″	12 x 1 box
100523598	Monomend® MaX RX-Z333-1 (2-0) HR26s (1/2 TP) 27″	12 x 1 box
100523600	Monomend® MaX RX-Z339-1 (2-0) HR37s (1/2 TP) 27″	12 x 1 box
100523601	Monomend® MaX RX-Z340-1 (0) HR37s (1/2 TP) 27″	12 x 1 box
100523602	Monomend® MaX RX-Z341-1 (1) HR37s (1/2 TP) 27″	12 x 1 box

Polymend® MT

Braided Mid-Term Absorbable Suture

DESCRIPTION A violet, braided, mid-term mid-term, synthetic absorbable suture that provides easy handling and excellent knot security providing wound support for 21 days and offering complete mass absorption in 56-70 days (0% initial tensile strength after 35 days). Absorbable synthetic suture comprised of PGLA (Polyglactin 910).

ITEM #	PRODUCT NAME	SUPPLIED
100510826	Polymend® MT B-J421-1 (5-0) DS19 (3/8 RC) 27″	12 x 1 box
100510827	Polymend® MT B-J315-1 (4-0) HR26 (1/2 TP) 27″	12 x 1 box
100510828	Polymend® MT B-J316-1 (3-0) HR26 (1/2 TP) 27″	12 x 1 box
100510829	Polymend® MT B-317-1 (2-0) HR26 (1/2 TP) 27″	12 x 1 box
100510850	Polymend® MT B-J332-1 (3-0) HR26s (1/2 TP) 27″	12 x 1 box
100510851	Polymend® MT B-J333-1 (2-0) HR26s (1/2 TP) 27″	12 x 1 box
100510852	Polymend® MT B-J340-1 (0) HR37s (1/2 TP) 27″	12 x 1 box
100510853	Polymend® MT B-J397-1 (4-0) DS19 (3/8 RC) 27″	12 x 1 box
100510854	Polymend® MT B-J398-1 (3-0) DS19 (3/8 RC) 27″	12 x 1 box
100510855	Polymend® MT B-J466-1 (2-0) HS37s (1/2 RC) 27″	12 x 1 box
100510856	Polymend® MT B-J467-1 (0) HS37s (1/2 RC) 27″	12 x 1 box
100510857	Polymend® MT B-J474-1 (1) HS37s (1/2 RC) 27″	12 x 1 box
100510858	Polymend® MT B-J452-1 (3-0) DS24 (3/8 RC) 27″	12 x 1 box
100510859	Polymend® MT B-J453-1 (2-0) DS24 (3/8 RC) 27″	12 x 1 box

NY-STĀ®

Monofilament Non-Absorbable Suture

DESCRIPTION NY-STĀ® is a black, monofilament, synthetic non-absorbable suture. Non-absorbable synthetic suture comprised of polyamide (Nylon).

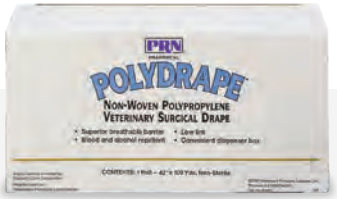
ITEM #	PRODUCT NAME	SUPPLIED
100503729	NY-STĀ® N-66430-1 (2-0) DS24 (3/8 RC) 30″	12 x 1 box
100503730	NY-STĀ® N-669-1 (3-0) DS24 (3/8 RC) 30″	12 x 1 box
30020	NY-STĀ® N-662-1 (4-0) DS19 (3/8 RC) 18″	12 x 1 box
30021	NY-STĀ® N-663-1 (3-0) DS24 (3/8 RC) 18″	12 x 1 box
30022	NY-STĀ® N-664-1 (2-0) DS24 (3/8 RC) 18″	12 x 1 box

PRO-STĀ® FLX

Monofilament Non-Absorbable Suture

DESCRIPTION PRO-STĀ® FLX is a blue, monofilament, synthetic non-absorbable suture. Non-absorbable synthetic suture comprised of 95% polypropylene and 5% polyethylene co-polymer.

ITEM #	PRODUCT NAME	SUPPLIED
100527367	PRO-STĀ® FLX P-8683 (4-0) DS19 (3/8 RC) 18″	12 x 1 box
100527368	PRO-STĀ® FLX P-8684 (3-0) DS24 (3/8 RC) 18″	12 x 1 box
100527369	PRO-STĀ® FLX P-8685 (2-0) DS24 (3/8 RC) 18″	12 x 1 box
100527380	PRO-STĀ® FLX P-8424 (0) HR37s (1/2 TP) 30″	12 x 1 box
100527381	PRO-STĀ® FLX P-8140 (1) HS40 (1/2 RC) 30″	12 x 1 box



Polydrape™

Surgical Drape

DESCRIPTION A proprietary, advanced 3-layer veterinary surgical drape that has auto-clavable properties (do not "flash" auto-clave), Polydrape™ Surgical Drape™ has excellent breathability. The non-woven polypropylene 3-layer structure readily allows gases and vapors to pass through. May also be sterilized using ethylene oxide procedure.

ITEM #	PRODUCT NAME	SUPPLIED
90300	Polydrape™ Surgical Drape	42" x 100 yard roll

Hexa-Caine™ Spray

Topical Anti-Itch Application

DESCRIPTION Topical anti-itch spray for dogs, cats and horses that includes wound licking deterrent. Contains: Lidocaine 2.46%, Benzethonium Chloride, no less than 0.2%. Also contains lanolin, aloe vera and denatonium benzoate (bitter flavoring agent to deter wound licking).

ITEM #	PRODUCT NAME	SUPPLIED
30023604	Hexa-Caine™ Topical Anti-Itch Spray	4 oz. spray bottle

Argon Medical Intracath™

Catheters

DESCRIPTION For use in large dogs, Argon Medical Intracath Catheters are made of Vialon™ Biomaterial with unique, self-contained, through-the-needle introducer system and wire stylet, allowing for rapid catheterization. The removable sheath minimizes touch contamination, and the stainless steel stylet assists in advancing catheter into the vein.

ITEM #	PRODUCT NAME	SUPPLIED
384900	Intracath™ Catheter, 16 G x 8.00 in.	50/box
384901	Intracath™ Catheter, 19 G x 8.00 in.	50/box
384902	Intracath™ Catheter, 22 G x 8.00 in.	50/box
384903	Intracath™ Catheter, 16 G x 12.00 in.	50/box
384904	Intracath™ Catheter, 19 G x 12.00 in.	50/box
384905	Intracath™ Catheter, 16 G x 24.00 in.	50/box
384906	Intracath™ Catheter, 19 G x 24.00 in.	50/box

Pet Pillers

Pill Dispenser

DESCRIPTION Administers capsules and various size tablets safely by protecting dogs or cats from injury with soft tip during dosing of medications and supplements.

ITEM #	PRODUCT NAME	SUPPLIED
30051399	Pet Piller	12 x 1 pillers per pack

Safe-Flow Dispensers

Oral Gel Dispenser

DESCRIPTION Designed to work with the Safe-Flow system for livestock, this device increases the ease of administration of gel nutritional supplements, such as Hi-Energy Supplement®, Magna Gel™ and High Potency Calcium Gel® by replacing messy caulking tube guns.

ITEM #	PRODUCT NAME	SUPPLIED
30052299	Safe-Flow Dispenser	12 x 1 dispenser

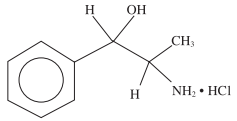
PROIN ER™

(phenylpropanolamine hydrochloride extended-release tablets)

For oral use in dogs only

CAUTION: Federal 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, 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. 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[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.

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.

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.[1]

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 (≥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 (6.0%)
Hypoglycemia	4 (3.3%)
Hypercalcemia	3 (2.5%)
Increased BUN	2 (1.7%)
Bradycardia (<60 bpm)	2 (1.7%)
Seizures/twitching	2 (1.7%)

[a] 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 (≥160 mmHg)[a]	19.5%	14.7%
Anorexia	16.3%	3.3%
Body weight loss (>5%)[b]	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%

[a] One or more systolic blood pressure readings of ≥160 mmHg.
[b] 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 (≥160 mmHg)[a]	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%

[a] Percent 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 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 www.fda.gov/reportanimalae.

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: 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.[2] 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.[3,4]

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_{max}), but the area under the concentration vs time curve to the last quantifiable concentration (AUC_{last}) was similar in both fed and fasted states. The small decrease in the post-prandial AUC_{last} appeared to be attributable to the corresponding increase in the terminal elimination rate constant under the fed conditions. The time to C_{max} (T_{max}) 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 ($t_{½}$) 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 phenylpropanolamine hydrochloride per tablet. PROIN ER is packaged in bottles containing 30 or 90 tablets.

REFERENCES:
[1] Watson R, et al. Ephedra alkaloids inhibit platelet aggregation. Blood coagulation and Fibrinolysis, 2010, 21:266-271.
[2] Richter K.P., Ling G.V. Clinical response and urethral pressure profile changes after phenylpropanolamine in dogs with primary sphincter incompetence. JAVMA, Vol. 187, No 6, September 15, 1985. 605-611.
[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.

Approved by FDA under NADA #141-517

Manufactured By: Pegasus Laboratories, Inc., Employee-Owned, Pensacola, FL 32514

PROIN®

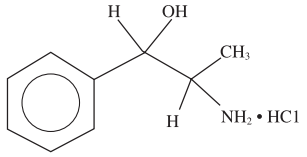
(phenylpropanolamine hydrochloride)

CHEWABLE TABLETS

For oral use in dogs only

Caution: Federal law 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, α-(1-aminoethyl)-, hydrochloride, (R*, S*)-, (±). The empirical formula is $C_9H_{13}NO \bullet HCl$ 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: 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.[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

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

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

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 (≥ 160 mmHg)[1]	34.6%
Body Weight loss (≥ 5%)	24.8%
Emesis	19.7%
Proteinuria	15.3%
Anorexia	10.2%
Diarrhea	6.4%
Lethargy	5.7%
Anxiety/behavior change/aggression	5.7%

[1] Percent of dogs with systolic blood pressures of ≥160 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, pilcerection,
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, pilcerection, 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 www.fda.gov/reportanimalae.

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 a-adrenergic agent which has been reported to increase urethral tone in dogs.2 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.[3,4]

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.5 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 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 pilled 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.

Approved by FDA under NADA #141-324.

PROIN® is a registered trademark of Pegasus Laboratories, Inc. 03-2023

References:

[1] Watson R, et al. Ephedra alkaloids inhibit platelet aggregation. Blood Coagulation and Fibrinolysis, 2010, 21: 266-271.
[2] Richter K.P., Ling G.V. Clinical response and urethral pressure profile changes after phenylpropanolamine in dogs with primary sphincter incompetence. JAVMA, Vol. 187, No 6, September 15, 1985. 605-611.
[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.
[5] Hussain, M.A., Aungst, B.J., Lam, G. and Shefter, E. Phenylpropanolamine pharmacokinetics in dogs after intravenous, oral, and oral controlled-release doses. Biopharm Drug Dispos, Vol. 8, No. 5, September-October 1987. 497-505.

Manufactured By: Pegasus Laboratories, Inc., Employee-Owned, Pensacola, FL 32514, USA

KBroVet®-CA1

(potassium bromide)

CHEWABLE TABLETS

Anti-epileptic for use in dogs only.

Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-544

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian. Use only as directed. It is a violation of Federal Law to use this product other than as directed in the labeling..

CONTRAINDICATIONS: KBroVet-CA1 should not be used in animals with a history of hypersensitivity to bromide.

DESCRIPTION: KBroVet-CA1 are flavored chewable tablets that contain potassium bromide (KBr). KBr is an odorless, colorless crystal or white crystalline powder or white granular solid with a pungent bitter saline taste. The molar mass of KBr is 119.002 g/mol, with high solubility in water, glycerol and ethanol.

Indication: KBroVet-CA1 (potassium bromide chewable tablets) are indicated for the control of seizures associated with idiopathic epilepsy in dogs.

DOSAGE AND ADMINISTRATION: The total recommended daily dosage range for oral administration is 25–68 mg/kg (11–31 mg/lb) of body weight. The dosage of KBroVet-CA1 should be adjusted based on monitoring of clinical response of the individual patient. KBroVet-CA1 may be dosed with or without food. Use of an initial loading dosage regimen may be considered on an individual patient basis, balancing the time required to achieve a therapeutic response while minimizing side effects.

WARNINGS:

User Safety Warnings
Not for human use. Keep out of reach of children. Contact a physician in case of accidental ingestion by humans.

Animal Safety Warnings
Not for use in cats.
Keep KBroVet-CA1 in a secured location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose

PRECAUTIONS: Dogs receiving KBr should be carefully monitored when changing diets, administering chloride-containing IV fluids, and administering concurrent medications. Careful monitoring is important in dogs that have a condition that may cause difficulty maintaining electrolyte balance.

Animals with decreased renal function may be predisposed to bromide toxicosis.

Some dogs may experience epileptic episodes that are unresponsive or refractory to KBr monotherapy and KBr alone may not be adequate treatment for every dog with idiopathic epilepsy.

The safe use of KBroVet-CA1 has not been evaluated in dogs that are intended for breeding, or that are pregnant or lactating. The safe use of KBr in neonates and young animals has not been established. Reproductive effects of KBr have been reported in other species. In dogs, ataxia, diarrhea, hematochezia, excessive salivation, shivering, skin lesions, stupor progressing to coma and death have been reported with a dose of 200 to 500 mg/kg a day for 4 to 26 weeks.

ADVERSE REACTIONS: In a retrospective field study of 51 dogs diagnosed with idiopathic epilepsy and receiving only KBr to control seizures associated with idiopathic epilepsy, adverse reactions were documented for the initial 60 days of treatment. Increased appetite, weight gain, vomiting/regurgitation and sedation were the most common clinical abnormalities documented in the 60 day period after start of KBr therapy (Table 1).

Table 1. Adverse Reactions Reported During Initial Dosing Phase (60 Day Period After Start of KBr Therapy)

Adverse Reaction	Number of Dogs with the Adverse Reaction
Increased Appetite	11
Weight Gain	8
Vomiting	5
Regurgitation	4
Sedation	3
Polydipsia	2
Ataxia	2
Polyuria	2
Weakness	2
Decreased Activity	1
Diarrhea	1
Disorientation	1
Lethargy	1
Partial Lack of Efficacy	1
Petit Mal Epilepsy	1
Seizure	1
Tiredness	1
Tremors	1

Adverse reactions were also documented during the 30 days prior to KBr sample submission. Weight gain, weakness, ataxia, and increased appetite were the most common adverse reactions documented during this time period (Table 2).

Table 2. Adverse Reactions Reported During Dosing Phase (30 Day Period Before KBr Sample Submission)

Adverse Reaction	Number of Dogs with the Adverse Reaction
Weight Gain	7
Weakness	5
Ataxia	4
Increased Appetite	4
Polydipsia	3
Sedation	3
Diarrhea	2
Polyuria	2
Regurgitation	2
Vomiting	2
Decreased Appetite	1
Disorientation	1
Loose Stool	1
Panting	1
Tremors	1

Adverse events associated with concurrent use of KBr with other antiepileptic drugs such as phenobarbital have been reported. Neurologic signs were the most common adverse event and included sedation, irritability, restlessness, depression, behavioral changes, ataxia, hind limb paresis, mydriasis, stupor, and coma. The neurologic signs were reported to be reversible.

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 reporting adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae

CLINICAL PHARMACOLOGY:
Mechanism of action: KBr is a halide salt that is thought to exert its antiepileptic activity by passing through neuronal chloride ion channels, thereby hyperpolarizing neuronal membranes, raising the seizure threshold, and stabilizing neurons against excitatory input from epileptic foci.

Pharmacokinetics: The pharmacokinetics of a multi-dose regimen of administration in normal dogs have been evaluated as described in a comprehensive literature review. In one study, KBr was administered at 30 mg/kg orally every 12 hrs for a period of 115 days. Serum, urine, and cerebrospinal fluid (CSF) bromide concentrations were measured at the onset of dosing, during the accumulation phase, steady-state, and after a subsequent dose adjustment. Median elimination half-life and steady-state serum concentration were 15.2 days and 245 mg/dL, respectively. Apparent total body clearance was 16.4 mL/day/kg and volume of distribution was 0.40 L/kg. The CSF:serum bromide ratio at steady-state was 0.77.

Distribution, Metabolism, and Elimination: Bromide distributes into the CSF and interstitial tissues of the brain and is actively transported out of the CNS via the choroid plexus. At pharmacological doses, the active transport mechanism is overwhelmed and bromide accumulates in the brain and CSF. Bromide is not metabolized by the liver and is eliminated unchanged, primarily by renal clearance. Increased dietary consumption of chloride can promote loss of bromide in the urine, leading to a lowering of serum bromide concentrations. Decreased chloride consumption will promote increased renal reabsorption of bromide, causing an increase in bromide elimination half-life in dogs.

REASONABLE EXPECTATION OF EFFECTIVENESS:
KBroVet-CA1 is conditionally approved pending a full demonstration of effectiveness.

Additional information for Conditional Approvals can be found by searching www.fda.gov for "animal conditional approval".

Two retrospective studies were used to determine the dose and demonstrate a reasonable expectation of effectiveness for KBroVet-CA1 for the control of seizures associated with idiopathic epilepsy in dogs.

In a dose determination retrospective study, the total daily oral dose of KBr given for ≥45 days (approaching steady-state conditions) was described. To be included in this study, cases were required to meet the following eligibility requirements: samples submitted for serum bromide concentration evaluation within the required date range (January 1, 2003 to August 31, 2010), and dogs were between ≥0.5 and ≤5.0 years of age, receiving only KBr to control seizures associated with idiopathic epilepsy, administered KBr once or twice daily for ≥45 days at the dose noted on the submission form, and the serum bromide concentration was ≥0.8 and ≤3.5 mg/mL.

A total of 284 case records (58.5% male and 41.6% female), with a mean age of 3.6 years (0.7-5.0 years) and a mean body weight of 20.5 kg (1.3-88.2 kg), were evaluated between January 1, 2003 to August 31, 2010. The mean total daily oral dose was 46.6 (±21.9) mg/kg with a range of 24.5-68.3 mg/kg. These results describe the total daily oral dose range to achieve serum bromide concentrations within 10% of the published therapeutic range (≥0.8 and ≤3.5 mg/mL)1,2 for dogs with idiopathic epilepsy.

A pilot retrospective study involving review of case records of 51 client-owned dogs was conducted to evaluate the effectiveness of KBr in dogs. This retrospective study evaluated case records of dogs previously receiving only KBr to control seizures associated with idiopathic epilepsy and for which blood samples had been analyzed to quantify serum bromide concentrations for the purpose of therapeutic drug monitoring.

Seizure counts, seizure count changes, seizure event days per month and seizure severity scores were tabulated for eligible cases, comparing the 30 day period before initial treatment with KBr and the 30 day period of steady state KBr dosing. Seizure count within an individual case was required to decrease by 50% or greater in order for the case to be classified as a seizure count success. Similarly, reduction in the number of seizure event days per month by ≥50% was required for the case to be classified as a seizure event day count success. No increase in severity score denoted an individual case treatment success for this variable. Of the 51 evaluable cases, 27 were determined as valid for safety and effectiveness data and 24 were determined to be valid for only safety data.

Of the 27 cases, 19 (70%) were defined as "success" and 8 (30%) were defined as "failures" based on seizure count results. Eighteen (67%) were defined as "success" and 9 (33%) were defined as "failures" based on seizure event day results. Seizure severity score decreased or did not change in 25 of the 27 cases evaluated for effectiveness. Overall, of the 27 dogs included in the effectiveness analysis, 18 (67%) were considered treatment successes and 9 (33%) were considered treatment failures.

ANIMAL SAFETY:
Safety was assessed in a systematic review of literature and a retrospective field study. Reversible neurologic signs were the most consistently reported adverse effect and were generally associated with adjunctive KBr treatment or high serum bromide concentrations. Adverse effects were also seen in some dogs with low serum bromide concentration. Dermatologic and respiratory abnormalities were rare in dogs. Evidence suggested that administration of KBr with food may alleviate gastrointestinal irritation and that monitoring for polyphagia, thyroid hormone abnormalities, and high serum bromide concentrations may be beneficial.

HOW SUPPLIED:
KBroVet-CA1 are flavored chewable, non-scored tablets containing 250 mg or 500 mg of potassium bromide per tablet. KBroVet-CA1 is packaged in bottles containing 60 or 180 tablets.

500 mg Tablet (60 ct) bottle NDC 49427-398-48
250 mg Tablet (60 ct) bottle NDC 49427-397-48
500 mg Tablet (180 ct) bottle NDC 49427-398-50
250 mg Tablet (180 ct) bottle NDC 49427-397-50

STORAGE CONDITIONS: Store at controlled room temperature 20-25°C (68-77°F).

Keep out of reach of children and animals.

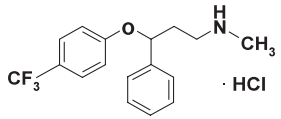
[1] Boothe DM. Anticonvulsant and other neurologic therapies. In: Boothe DM, Ed. SmallAnimal clinical pharmacology and therapeutics. Philadelphia: WB Saunders Co.,2001; 431-456
[2] Dewey CW. Anticonvulsant therapy in dogs and cats. Vet Clin North Am Small Anim Pract 2006; 36:1107-1127.

Manufactured By: Pegasus Laboratories, Inc., Employee-Owned, Pensacola, FL 32514, USA

RECONCILE®
(fluoxetine hydrochloride)
CHEWABLE TABLETS

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Description: RECONCILE is a chewable, flavored tablet that contains fluoxetine hydrochloride. RECONCILE chewable tablets are available in 8, 16, 32, and 64 mg tablet strengths for oral administration to dogs. The active ingredient in RECONCILE chewable tablets is fluoxetine hydrochloride, a selective serotonin reuptake inhibitor (SSRI). The molecular weight of fluoxetine is 345.79. The structural formula is depicted below.



fluoxetine hydrochloride
$C_{17}H_{18}F_3NO{\cdot}HCl$

Indications: RECONCILE chewable tablets are indicated for the treatment of canine separation anxiety in conjunction with a behavior modification plan.

Dosage and Administration: The recommended dose of RECONCILE chewable tablets is 1-2 mg/kg (0.5-0.9 mg/lb) administered once daily, in conjunction with a behavior modification plan. A typical behavior modification plan consists of the pet owner implementing standard training techniques based on principles such as rewarding appropriate behavior; coming and going in a manner that does not elicit inappropriate responses from the dog; and teaching the dog to be content while alone.

Table 1: Recommended Dose of RECONCILE Chewable Tablets

Dog Weight (lb)	Dog Weight (kg)	No. of Tablets/Day	Tablet Strength (mg)
8.8 - 17.6	4.0 - 8.0	1	8
17.7 - 35.2	8.1 - 16.0	1	16
35.3 - 70.4	16.1 - 32.0	1	32
70.5 - 140.8	32.1 - 64.0	1	64

The effectiveness and safety of RECONCILE chewable tablets was demonstrated in a field study in client-owned dogs (see **EFFECTIVENESS** and **ADVERSE REACTIONS**). At the end of the 8-week study, 73% of dogs treated with RECONCILE chewable tablets showed significant improvement (p=0.010), as compared to behavior modification alone (51%). During the course of therapy, 42% of dogs showed improvement within the first week, which was significantly greater (p=0.005) than with behavior modification alone (18%). The patient's response to therapy should be monitored. If no improvement is noted within 8 weeks, case management should be reevaluated.

The effectiveness and clinical safety of RECONCILE chewable tablets for long-term use (i.e. for more than 8 weeks) has not been evaluated. RECONCILE chewable tablets were evaluated at the recommended label dose for one year in a laboratory safety study in dogs (see **ANIMAL SAFETY**).

Professional judgment should be used in monitoring the patient's response to therapy to determine the need to continue treatment with RECONCILE chewable tablets beyond 8 weeks. To discontinue therapy, it is not necessary to taper or reduce doses because of the long half-life of this product. Continued behavioral modification is recommended to prevent recurrence of the clinical signs.

RECONCILE chewable tablets are readily consumed by dogs or can be administered like other tablet medications, and can be given with or without food.

Professional discretion should be used in determining the need for dose reduction in the event of a possible adverse reaction. Approximately half of patients tolerate a return to the previous dose after 1-2 weeks on a reduced schedule (see **ADVERSE REACTIONS**).

If a dose is missed, the next scheduled dose should be administered as prescribed. Do not increase or double the dose.

Contraindications:
RECONCILE chewable tablets are contraindicated for use in dogs with epilepsy or a history of seizures. RECONCILE chewable tablets should not be given concomitantly with drugs that lower the seizure threshold (e.g., phenothiazines such as acepromazine or chlorpromazine).

RECONCILE chewable tablets should not be given in combination with a monoamine oxidase inhibitor (MAOI) [e.g., selegiline hydrochloride (L-deprenyl) or amitraz], or within a minimum of 14 days of discontinuing therapy with an MAOI.

RECONCILE chewable tablets are contraindicated in dogs with a known hypersensitivity to fluoxetine HCl or other SSRIs.

Because fluoxetine and its major metabolite, norfluoxetine, have long half-lives, a 6-week washout interval should be observed following discontinuation of therapy with RECONCILE chewable tablets prior to the administration of any drug that may adversely interact with fluoxetine or norfluoxetine.

Warnings: Not for use in humans. **Keep out of reach of children**. In case of accidental ingestion seek medical attention immediately. In humans, the most common symptoms associated with over dosage include seizures, somnolence, nausea, tachycardia, and vomiting. In case of ingestion by a human, contact a physician immediately. For a copy of the Safety Data Sheet (SDS) or to report adverse reactions call 1-800-874-9764.

Precautions:
RECONCILE chewable tablets are not recommended for the treatment of aggression. RECONCILE chewable tablets have not been clinically tested for the treatment of other behavioral disorders. Studies to determine the effects of RECONCILE chewable tablets in breeding, pregnant, or lactating dogs and in patients less than 6 months of age have not been conducted.

Seizures may occur in dogs treated with RECONCILE chewable tablets, even in dogs without a history of epilepsy or seizures (see **ADVERSE REACTIONS**).

Before prescribing RECONCILE chewable tablets, a comprehensive physical examination should be conducted to rule out causes of inappropriate behavior unrelated to separation anxiety. The examination should include a thorough history and assessment of the patient's household environment and standard practice laboratory tests as appropriate for the patient's age and health status. Veterinarians should be familiar with the risks and benefits of the treatment of behavioral disorders in dogs before initiating therapy. Inappropriate use of RECONCILE chewable tablets, i.e. in the absence of a diagnosis or without concurrent behavior modification, may expose the animal to unnecessary adverse reactions and may not provide any lasting benefit of therapy.

RECONCILE chewable tablets have not been evaluated with drugs that affect the cytochrome P450 enzyme system. RECONCILE chewable tablets should be used with caution when co-administered with any drug that affects the cytochrome P450 enzyme system (for example, ketaconazole). Studies to assess the interaction of RECONCILE chewable tablets with tricyclic antidepressants (TCAs) (for example, amitriptyline and clomipramine) have not been conducted. The minimum washout period to transition dogs from TCAs to RECONCILE chewable tablets has not been evaluated. Published pharmacokinetic data demonstrates that TCAs are cleared 4 days following discontinuation.[1,2]

Adverse Reactions:
In two North American multi-site field studies, which included a total of 427 dogs, the following adverse reactions were observed:

Seizures:
In one study, one of 112 dogs in the control group and three of 117 dogs that received RECONCILE chewable tablets experienced the serious adverse reaction of seizures. One of the three dogs treated with RECONCILE chewable tablets experienced two seizures 10 days after the end of therapy. Despite escalating phenobarbital doses, the seizures continued and this dog died in status epilepticus approximately six months after the first seizure. Another of the three dogs treated with RECONCILE chewable tablets had experienced one seizure approximately 1½ years prior to study enrollment immediately after receiving head trauma. No additional seizures were reported to have occurred until 45 days after concluding treatment with RECONCILE chewable tablets. During the 1½-year period since the second seizure, this dog's seizure activity increased from single seizures to cluster seizures despite increasing doses of phenobarbital and the addition of oral potassium bromide and rectal diazepam. The third dog treated with RECONCILE chewable tablets and the control dog experienced one seizure 24 days and 35 days, respectively, after the start of therapy; no anticonvulsant therapy was initiated and no further seizures were reported in either dog.

In the second study, one of 99 dogs treated with RECONCILE chewable tablets and one of 99 dogs treated with the control tablet experienced the serious adverse reaction of seizures 9 and 27 days, respectively, after initiation of therapy. The dog treated with RECONCILE chewable tablets was subsequently diagnosed with vestibular disease and the control dog had a history of recurrent hind leg weakness.

In a European multi-site study, 234 dogs were treated with daily doses of fluoxetine chewable tablets ranging from 0.25 mg/kg to 4 mg/kg. One dog treated with a daily dose of 0.4 mg/kg for one month experienced one seizure one week after discontinuing therapy. No anticonvulsant therapy was initiated and no further seizures were reported.

Weight loss:
Of the dogs in the two North American field studies with body weight measurements throughout the study (n=196 and n=185 in the RECONCILE chewable tablets and control group, respectively), a 5% or greater weight loss (when compared to initial, pre-study body weight) was observed in 58 (29.6%) of dogs treated with RECONCILE chewable tablets and 24 (13.0%) of dogs in the control group. No dogs were withdrawn from clinical studies due to weight loss alone. The following table shows the number of dogs with weight loss, stratified by percent weight loss relative to initial body weight.

[1] Plumb DC. Amitriptyline. Veterinary Drug Handbook 5th Edition (Pocket Edition). Iowa State Press. Ames, IA. Page 39, 2002.
[2] Hewson CJ, et.al. The pharmacokinetics of clomipramine and desmethylclomipramine in dogs: parameter estimates following a single oral dose and 28 consecutive daily doses of clomipramine. J Vet Pharmacol Therap 21:214-222, 1998.

Table 2: Dogs with Weight Loss (stratified by percent loss relative to initial body weight)

Treatment Group	≥ 5% to < 10% Number (%)	≥ 10% to < 15% Number (%)	≥ 15% Number (%)
RECONCILE chewable tablets	44 (22.5%)	13 (6.6%)	1[a] (0.5%)
Control	20 (10.8%)	4 (2.2%)	0 (0%)

[a] This dog lost 20% of its initial body weight and was the same dog that died in status epilepticus.

Other adverse reactions: Additional adverse reactions observed in dogs treated with RECONCILE chewable tablets at a rate of 1% or greater were::

Table 3: Adverse Reactions Reported in the North American Field Studies

	RECONCILE Chewable Tablets, N=216		Control,* N=211	
Adverse Reaction	n	%	n	%
Calm/Lethargy/Depression	71	32.9	22	10.4
Decreased Appetite	58	26.9	13	6.2
Vomiting	37	17.1	28	13.3
Shaking/Shivering/Tremor	24	11.1	4	1.9
Diarrhea	21	9.7	17	8.1
Restlessness	16	7.4	8	3.8
Excessive Vocalization (Including Whining)	13	6.0	7	3.3
Aggression	9	4.2	13	6.2
Otitis Externa	6	2.8	2	0.9
Disorientation	5	2.3	1	0.5
Incoordination	5	2.3	0	0.0
Constipation	3	1.4	0	0.0
Excessive Salivation	3	1.4	4	1.9

*** The control group received the tablet formulation without fluoxetine.**

Dose Reduction:
Twenty dogs in the RECONCILE chewable tablet group and five dogs in the control group required a reduction in dose due to unacceptable adverse reactions, generally anorexia, vomiting, shaking and depression. Lowering the dose eliminated or reduced the severity of these adverse reactions in the RECONCILE chewable tablet group only. Resumption of the full dose of RECONCILE chewable tablets resulted in a return of the initial adverse reactions in approximately half of the affected dogs. The majority of these adverse reactions were intermittent and mild. However, one dog experienced recurrence of severe adverse reactions, which necessitated withdrawal from the study for that dog. Additionally, two dogs required a second dose reduction of RECONCILE chewable tablets. Effectiveness was maintained in a majority of those dogs in which a dose reduction was necessary.

Post Approval Experience (Rev. 2010):
The following adverse events are based on post-approval adverse drug experience reporting with RECONCILE chewable tablets. Not all adverse reactions 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 this data.

The following adverse events are listed in decreasing order of reported frequency: decreased appetite, depression/lethargy, shaking/shivering/tremor, vomiting, restlessness and anxiety, seizures, aggression, diarrhea, mydriasis, vocalization, weight loss, panting, confusion, incoordination, and hypersalivation.

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/reportanimalae.

Clinical Pharmacology:

Fluoxetine exerts its effect by inhibiting the reuptake of serotonin at the pre-synaptic neuron. Fluoxetine does not act as a sedative. Fluoxetine is well absorbed after oral administration (~72%). It is largely metabolized in the liver by cytochrome P-450 enzyme system to norfluoxetine, an equipotent SSRI that contributes to the efficacy of RECONCILE chewable tablets.

After a single dose, and also at steady state, calculations were made as follows:

Table 4: Single Dose* Pharmacokinetic Parameters of Fluoxetine Hydrochloride (mean ± standard error).

	$AUC_{0-\infty}$ (µg•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$T_{1/2}$ Range (hr)
Fluoxetine	1.388 (±0.137)	126.6 (±12.3)	1.8 (±0.2)	6.2 (±0.8)	3.0-12.9
Norfluoxetine	11.44 (±0.74)	138.3 (±9.6)	12.8 (±1.7)	49 (±3)	33.0-64.0

*approximately 2 mg/kg body weight

In a 21-day study, fluoxetine was administered daily at a dose of 0.75, 1.5 and 3.0 mg/kg to laboratory Beagles. The maximum plasma concentration (Cmax) and area under the plasma concentration time curve (AUC) for fluoxetine were approximately dose proportional between 0.75 and 1.5 mg/kg, with a greater than dose proportional increase at 3 mg/kg. Norfluoxetine Cmax and AUC were generally dose proportional.

Although steady state appeared to be reached within 10 days in the 21-day study, a continuous increase in trough concentrations was observed in a one year, multiple-dose laboratory safety study. In this study, dogs administered a 1 mg/kg dose of fluoxetine had plasma fluoxetine concentrations that continued to increase over the one-year dosing period. A similar increase in concentrations was observed with norfluoxetine. This phenomenon was not observed at higher doses. During the one-year dosing interval and the subsequent two-month recovery period, there were no changes in the nature and frequency of adverse reactions observed as compared to those seen by Day 28 of fluoxetine administration.

Effectiveness:
In one randomized multi-centered, double-blinded, vehicle-
controlled study of 8 weeks duration, 229 dogs were evaluated at 34 investigative sites in the United States and Canada. One hundred seventeen dogs were randomized to 1-2 mg/kg/day of RECONCILE chewable tablets and 112 dogs were randomized to the control group. Both groups underwent concurrent behavior modification. In seven of the eight weeks, the percentage of dogs with improved overall separation anxiety scores was significantly higher ($p < 0.05$) among dogs treated with RECONCILE chewable tablets compared to dogs that received the control tablet. At the end of the study, 73% of dogs treated with RECONCILE chewable tablets showed significant improvement (p=0.010) as compared to 51% of dogs treated with behavior modification alone.

Dogs treated with RECONCILE chewable tablets also showed improvement in destructive behavior, excessive vocalization, and restlessness over dogs that received the control tablet. In addition, dogs in both groups experienced improvement in inappropriate urination, inappropriate defecation, excessive salivation, excessive licking/grooming, shaking/shivering and depression. Overall separation anxiety severity scores improved more rapidly for dogs taking RECONCILE chewable tablets than those dogs receiving the control tablet. The same effect was also noted for the individual scores for excessive vocalization and depression.

Animal Safety:
In a one-year laboratory safety study, dogs were dosed daily at 1, 4.5, and 20 mg/kg/day of a gelatin capsule filled with fluoxetine powder. Based upon the results of a relative bioavailability study comparing the fluoxetine-filled capsule versus the RECONCILE chewable tablets, the corresponding equivalent doses were 0.87, 3.9 and 17.4 mg/kg/day of RECONCILE chewable tablets (where the average ratio of fluoxetine AUC values for RECONCILE chewable tablets/fluoxetine-filled capsule = 1.15).

Three of five female dogs in the 20 mg/kg group, died or were euthanized during the first six months of the study. The high dose was decreased to 10 mg/kg/day (equivalent to 8.7 mg/kg/day of RECONCILE chewable tablets) for the last six months of the treatment, and all remaining dogs completed the study. One dog in the 1 mg/kg group (equivalent to 0.87 mg/kg/day of RECONCILE chewable tablets) and two dogs in the 20 mg/kg group (equivalent to 17.4 mg/kg/day of RECONCILE chewable tablets) experienced a seizure. Aggressive behavior, ataxia, salivation at dosing, hyperesthesia, nystagmus, thin body condition, weakness, lethargy, diarrhea and head tilt were also noted in the high dose group. Anorexia, tremors, decreased pupillary light response, mydriasis, vomiting, and decreased weight gain were observed in all treatment groups, but occurred more frequently in the high dose group. With the exception of decreased weight gain, all abnormal observations resolved by the end of a two-month recovery period. Evidence of phospholipidosis was noted in the lung, liver, adrenal glands, lymph nodes, spleen, retina and white blood cells of all groups, which resolved during the recovery period. Fluoxetine caused no marked or consistent effects on hematology, blood chemistries or urinalysis. Bradycardia was absent on the electrocardiogram in the control and lowest dose groups, but was mildly present in a dose-dependent manner in the two higher dose groups. There were no effects noted on gross organ examination.

Storage Information:
Store at 20-25°C (68-77°F). Excursions permitted between 15-30°C (59-86°F).
Do not remove desiccant from the bottle.
Completely close bottle between uses.

How Supplied:
RECONCILE is supplied in 8mg, 16mg, 32mg and 64mg strengths; as 30 or 90 tablets per bottle, with a child-resistant cap.

Approved by FDA under NADA #141-272

Manufactured By: Pegasus Laboratories, Inc., Employee-Owned, Pensacola, FL 32514

ReBalance®

(sulfadiazine and pyrimethamine)

ANTIPROTOZOAL ORAL SUSPENSION

Approved by FDA under NADA 141-240

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

DESCRIPTION: ReBalance Antiprotozoal Oral Suspension is supplied in 946.4 mL (1 quart) bottles. Each mL of **ReBalance Antiprotozoal Oral Suspension** contains 250 mg sulfadiazine (as the sodium salt) and 12.5 mg pyrimethamine.

INDICATIONS: ReBalance Antiprotozoal Oral Suspension is indicated for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by Sarcocystis neurona.

DOSAGE AND ADMINISTRATION: ReBalance Antiprotozoal Oral Suspension is to be administered at a dose of 20 mg/kg sulfadiazine and 1 mg/kg pyrimethamine daily or 4 mL of **ReBalance Antiprotozoal Oral Suspension** per 110 lb. (50 kg) of body weight once per day. The duration of treatment is dependent upon clinical response, but the usual treatment regimen ranges from 90 to 270 days.

Administer orally by suitable dosing syringe at least one hour prior to feeding with hay or grain. Insert nozzle of syringe through the interdental space and deposit the dose on the back of the tongue by depressing the plunger. Shake well before each use.

CONTRAINDICATIONS: The use of **ReBalance Antiprotozoal Oral Suspension** is contraindicated in horses with known hypersensitivity to sulfonamide drugs or pyrimethamine.

WARNINGS: For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of the reach of children.

PRECAUTIONS: Prior to treatment with **ReBalance Antiprotozoal Oral Suspension**, EPM should be distinguished from other diseases that may cause ataxia in horses. Injuries or lameness may also complicate the evaluation of an animal with EPM. In most instances, ataxia due to EPM is asymmetrical and affects the front and/or the hind limbs.

Treatment may cause generalized bone marrow suppression, anemia, leukopenia, neutropenia and thrombocytopenia. A complete blood count (CBC) should be performed monthly to monitor horses for development of these conditions. The administration of the drug may need to be discontinued and/or treatments for bone marrow suppression initiated.

Worsened neurologic deficits (treatment crisis) may be observed during a period beginning with the first few days of treatment with **ReBalance Antiprotozoal Oral Suspension** and ranging out to 5 weeks. This neurologic deficit exacerbation may be the result of an inflammatory reaction to the dying parasites in the CNS tissue.

The safe use of **ReBalance Antiprotozoal Oral Suspension** in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. The safety of ReBalance Antiprotozoal Oral Suspension with concomitant therapies in horses has not been evaluated.

ADVERSE REACTIONS: Seventy-five horses (37 horses in the 1X group; 38 horses in the 2X group) that were treated with test article for at least 90 days were evaluated for adverse reactions.

Bone marrow suppression:
Anemia: ReBalance Antiprotozoal Oral Suspension administration caused overall anemia (classification of anemia based on RBC, Hgb, and PCV/HCT values) in 12% of the observations in the 1X group and 21% of the observations in the 2X group. In the 1X group, anemia was noted in 22%, leukopenia in 19%, neutropenia in 5%, and thrombocytopenia in 3% of the cases. In the 2X group, anemia was noted in 58%, leukopenia in 55%, neutropenia in 29% and thrombocytopenia in 5% of the cases. The incidence of bone marrow suppression in the 2X treatment group was two or more times that of the 1X group and the degree of suppression was more serious (mild to severe vs. mild to moderate). Because of these blood dyscrasias, test article was interrupted over four times more often in horses treated at the 2X dosage than those treated at 1X, although both groups were off treatment for about the same amount of time (approximately 20% of the treatment period). In some instances of bone marrow suppression, diet was supplemented with folinic acid.

GI: Anorexia was observed in two horses in the 1X group and one horse in the 2X group. One horse in the 1X group and one horse in the 2X group were observed to be off feed. Observations of anorexia and decreased appetite occurred predominantly during the first 90 days of the treatment period. Observations of anorexia/decreased appetite in two of the above-referenced cases were due to unrelated illnesses. Loose stools were observed in three horses in the 1X group and five in the 2X group. The majority of these observations occurred in the first thirty days of treatment.

Diarrhea was observed in one horse in the 2X group on Day 4 of the study. The appearance of loose stool/diarrhea observations was self-limiting and resolved without treatment or discontinuation of test article. Brief, mild colic was observed in three cases (one in the 1X group and two in the 2X group). Colic was treated conservatively or not at all and resolved without sequelae.

Integument: Urticaria was observed in one horse in the 1X group and two horses in the 2X group. One horse was treated topically, two were untreated. All cases resolved without sequelae.

Treatment crisis (marked worsening of the neurological condition) was reported in one horse in the 1X treatment group.

Depression/lethargy was observed infrequently, occurred during the early part of the study in both groups and was primarily associated with the EPM syndrome. In one case, depression was associated with acute onset of a liver disorder.

Seizure: One horse in the 1X treatment group suffered from seizures. Seizure activity may be associated with CNS damage from EPM.

CLINICAL PHARMACOLOGY: Sulfonamides (a specific group of antimicrobial agents) and pyrimethamine are two different antimicrobial agents which inhibit folic acid synthesis at two different sites, in the same synthetic pathway. The combination of a sulfonamide and pyrimethamine is synergistic, with the drug combination having an antiprotozoal effect.

EFFECTIVENESS SUMMARY: A field effectiveness study was conducted at eight sites with eight investigators across the United States. The study was conducted using historical controls. In this study, each animal's response to treatment was compared to its pre-treatment values. The following standardized overall neurological dysfunction (OND) scale was used to grade the horses:

0 = Clinically normal. No detectable dysfunction.
1 = Slight deficit. Dysfunction barely perceptible.
2 = Moderate deficit. Dysfunction easily detectable.
3 = Marked deficit. Dysfunction strikingly conspicuous.
4 = Severe deficit. Profound dysfunction.
5 = Recumbent.

Ninety-seven horses were randomly assigned to one of two treatment groups and administered a daily oral dose of **ReBalance Antiprotozoal Oral Suspension** for a minimum of 90 days. The two treatment groups were as follows:

(1) 1X labeled dose, 20 mg/kg sulfadiazine and 1 mg/kg pyrimethamine (48 horses); or

(2) 2X dose, twice the labeled dose, 40 mg/kg sulfadiazine and 2 mg/kg pyrimethamine (49 horses).

A physical examination and neurological evaluation and complete blood profile were conducted at the end of each 30-day treatment period for the first 90 days of treatment.

At the end of the 90-day treatment period, a videotape recording of the neurological condition and CSF and serum sample immunoblot and protein electrophoresis analyses were made. Based on the degree of clinical improvement and results of the CSF immunoblot analysis on test day 90, treatment in 30-day increments up to a period of 180 days was continued. In fourteen cases, the treatment was extended beyond 180 days (up to 270 days). A 30-day follow-up evaluation was made following cessation of treatment.

Treatment success was defined as: (1) a horse that became CSF Western Blot Test negative with or without clinical improvement; and (2) a horse that remained CSF Western Blot Test positive but demonstrated marked clinical improvement (two or more grade improvement from baseline OND score).

Only the 1X dose was evaluated for effectiveness due to the toxicity (bone marrow suppression) seen at the 2X dose. Of the forty-eight horses assigned to the 1X group, 26 horses completed the study. Based on the improvement in the OND scores and/or a negative CSF immunoblot, 16 out of 26 horses (61.5%) were considered successes. Five of the 26 horses (19.2%), had a negative CSF immunoblot by day 150 of the study. Three of these five horses were also clinical successes based on the improvement in OND scores. Fourteen of the 26 horses (53.8%) were corroborated as successes by masked expert evaluation of videotapes.

ANIMAL SAFETY: ReBalance Antiprotozoal Oral Suspension was administered to ten horses (5 males and 5 females) at a dosage of 8 mL/50 kg (110 lbs) a day (2X the labeled dose) for 92 days. Four horses (2 males and 2 females) were untreated controls.

Complete physical examinations, CBCs and serum chemistry values were determined on test day (TD) minus 14, TD minus 7, TD 0, biweekly throughout the 92 day treatment period and 14 and 29 days following the end of treatment.

Declines in RBC, HCT, Hgb and PCV were greater in the treated group and reached statistical significance. Twenty-nine days after cessation of treatment, blood parameter values returned to baseline levels. No clinical signs of anemia were observed in either group.

Most serum chemistry values remained within normal limits throughout the study in both groups. Alkaline phosphatase (ALP) values were evaluated (slightly above the upper end of the normal range) in three treated horses on study days 84 and 105.

Loose stools, along with infrequent diarrhea, were noted in the treatment group. The conditions were transient and required no medical intervention.

A depressed appetite of 1 to 2 days duration occurred infrequently in all but one of the treated horses. One horse became anorexic and required a change in diet.

ReBalance Antiprotozoal Oral Suspension administered at 2X the recommended label dose for 92 days resulted in clinical signs of toxicity including transient anemia and loose stools; however, medical intervention was not necessary.

STORAGE: Store at 20°C-25°C (68°F-77°F), excursions permitted between 15°C-30°C (59°F-86°F). Protect from freezing.

HOW SUPPLIED: Each mL of **ReBalance Antiprotozoal Oral Suspension** contains 250 mg sulfadiazine (as the sodium salt) and 12.5 mg pyrimethamine and is available in 946.4 mL (1 quart), multiple dose, child-resistant, screw-capped bottles.

For a Safety Data Sheet (SDS) or to report Adverse Reactions, call Pegasus Laboratories, Inc. 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/reportanimalae.

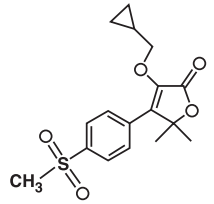
Manufactured By: Pegasus Laboratories, Inc., Employee-Owned, Pensacola, FL 32514, USA

FIROCOXIB CHEWABLE TABLETS FOR DOGS

For oral use in dogs only.

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

Description:
Firocoxib Chewable Tablets for Dogs belongs to the coxib class of non-narcotic, non-steroidalanti-inflammatory drugs. Firocoxib is a white crystalline compound described chemically as 3-(cyclopropyl-methoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethylfuranone. The empirical formula is C17H20O5S, and the molecular weight is 336.4. The structural formula is shown below:



Pharmacokinetics:
The absolute bioavailability of Firocoxib Chewable Tablets for Dogs is approximately 38% when administered as a 5 mg/kg oral dose to fasted adult dogs. Firocoxib is rapidly cleared from the blood via hepatic metabolism and fecal excretion (CLsystemic = ~0.4 L/hr/kg). Despite a high level of plasma protein binding (96%), firocoxib exhibits a large volume of distribution (Vd$_{ss}$ of total drug = ~4.6 L/kg) and a terminal elimination half life of 7.8 hours (%CV = 30%). The oral drug absorption process is highly variable among subjects. Co-administration of firocoxib with food delays drug absorption (Tmax from 1 to 5 hours) and decreases peak concentrations (Cmax from 1.3 to 0.9 mcg/mL). However, food does not affect the overall oral bioavailability at the recommended dose.

Indications:
Firocoxib Chewable Tablets for Dogs are indicated for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain and inflammationassociatedwithsoft tissue and orthopedic surgery in dogs.

Dosage and Administration:
Always provide the Client Information Sheet with prescription. Carefully consider thepotential benefits and risks of Firocoxib Chewable Tablets for Dogs and other treatment options before deciding to use Firocoxib Chewable Tablets for Dogs. Use the lowest effective dose for the shortest duration consistent with individual response. The recommended dosage of Firocoxib Chewable Tablets for Dogs for oral administration in dogs is 2.27 mg/lb (5.0 mg/kg) body weight once daily as needed for osteoarthritis and for 3 days as needed for postoperative pain and inflammation associated with soft-tissue and orthopedic surgery. The dogs can be treated with Firocoxib Chewable Tablets for Dogs approximately two hours prior to surgery. The tablets are scored and dosage should be calculated in half tablet increments. Firocoxib Chewable Tablets for Dogs can be administered with or without food.

Contraindications:
Dogs with known hypersensitivity to firocoxib should not receive Firocoxib Chewable Tablets for Dogs.

Warnings:
Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

Keep Firocoxib Chewable Tablets for Dogs in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.
For oral use in dogs only. Use of this product at doses above the recommended 2.27 mg/lb (5.0 mg/kg) in puppies less than seven months of age has been associated with serious adverse reactions, including death (see Animal Safety). Due to tablet sizes and scoring, dogs weighing less than 12.5 lb (5.7 kg) cannot be accurately dosed.
All dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum baseline data is recommended prior to and periodically during administration of any NSAID.
Owners should be advised to observe for signs of potential drug toxicity (see Adverse Reactions and Animal Safety) and be given a Client Information Sheet about Firocoxib Chewable Tablets for Dogs.

Contact Information:
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Pegasus Laboratories, Inc. at 1-800-874-9764 or www.pmpharmacal.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Precautions:
This product cannot be accurately dosed in dogs less than 12.5 pounds in body weight.

Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with renal, gastrointestinal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached and monitored. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to produce gastrointestinal ulceration and/or gastrointestinal perforation, concomitant use of Firocoxib Chewable Tablets for Dogswith other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. The concomitant use of protein-bound drugs with Firocoxib Chewable Tablets for Dogs has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant, and behavioral medications.The influence of concomitant drugs that may inhibit the metabolism of Firocoxib Chewable Tablets for Dogs has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

If additional pain medication is needed after the daily dose of Firocoxib Chewable Tablets for Dogs, a non-NSAID class of analgesic may be necessary.

Appropriate monitoring procedures should be employed during all surgical procedures. Anesthetic drugs may affect renal perfusion, approach concomitant use of anesthetics and NSAIDs cautiously. The useofparenteral fluidsduringsurgeryshouldbe considered to decrease potential renal complications when using NSAIDs perioperatively.

The safe use of Firocoxib Chewable Tablets for Dogs in pregnant, lactating or breeding dogs has not been evaluated.

Adverse Reactions:
Osteoarthritis: In controlled field studies, 128 dogs (ages 11 months to 15 years) were evaluated forsafety when given firocoxibchewable tablets at a dose of 2.27 mg/lb (5.0 mg/kg) orally once daily for 30 days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed adverse reactions during the study.

Precautions: This product cannot be accurately dosed in dogs less than 12.5 pounds in body weight.

Consider appropriate washout times when switching from one NSAID to another or when switching from corticosteroid use to NSAID use.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with renal, gastrointestinal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached and monitored. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effectsmay result in clinically significantdisease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to produce gastrointestinal ulceration and/or gastrointestinal perforation, concomitant use of Firocoxib Chewable Tablets for Dogswith other anti-inflammatorydrugs, suchasNSAIDs or corticosteroids, should be avoided. The concomitant use of protein-bound drugs with Firocoxib Chewable Tablets for Dogs has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant, and behavioral medications. Theinfluenceofconcomitantdrugs that may inhibit the metabolism of Firocoxib Chewable Tablets for Dogs has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

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The safe use of Firocoxib Chewable Tablets for Dogs in pregnant, lactating or breeding dogs has not been evaluated.

Adverse Reactions:
Osteoarthritis: In controlled field studies, 128 dogs (ages 11 months to 15 years) were evaluated forsafety when given firocoxibchewable tabletsata dose of 2.27 mg/lb (5.0 mg/kg) orally once daily for 30 days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed adverse reactions during the study.

Adverse Reactions Seen in the U.S. Field Studies

Adverse Reactions	Firocoxib n = 128	Active Control n = 121
Vomiting	5	8
Diarrhea	1	10
Decreased Appetite or Anorexia	3	3
Lethargy	1	3
Pain	2	1
Somnolence	1	1
Hyperactivity	1	0

Firocoxib chewable tablets were safely used during field studies concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics.

Soft Issue:
In controlled field studies evaluating soft-tissue post operative pain and inflammation, 258 dogs (ages 10.5 weeks to 16 years) were evaluated for safety when given firocoxib chewable tablets at a dose of 2.27 mg/lb (5.0 mg/kg) orally approximately 2 hours prior to surgery and once daily thereafter for up to two days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed reactions during the study.

Adverse Reactions Seen in the Soft-tissue Surgery Postoperative Pain Field Studies

Adverse Reactions	Firocoxib n = 127	Active Control n = 131
Vomiting	5	6
Diarrhea	1	1
Bruising at Surgery Site	1	1
Respiratory Arrest	1	0
SQ Crepitus in Rear Leg and Flank	1	0
Swollen Paw	2	0

Sham-Dosed Pilled

Orthopedic Surgery:
In a controlled field study evaluating orthopedic postoperative pain and inflammation, 226 dogs of various breeds, ranging in age from 1 to 11. 9years in the firocoxib-treated groups and 0.7 to 17 years in the control group were evaluated for safety. Of the 226 dogs, 118 were given firocoxib chewable tablets at a dose of 2.27mg/lb (5.0 mg/kg) orally approximately 2 hours prior to surgery and once daily thereafter for a total of three days. The following adverse reactions were observed. Dogs may have experienced more than one of the observed reactions during the study.

Adverse Reactions Seen in the Orthopedic Surgery Postoperative Pain Field Study

Adverse Reactions	Firocoxib n = 118	Active Control n = 108
Vomiting	1	0
Diarrhea	2**	1
Inappetence/Decreased Appetite	2	3
Pyrexia	0	1
Incision Swelling, Redness	9	5
Oozing Incision	2	0

A case may be represented in more than one category.

*Sham-dosed (pilled).

**One dog had hemorrhagic gastroenteritis.

Post-Approval Experiences (Rev. 2009): The following adverse reactions are based on post-approval adverse drug event reporting. The categories are listed in decreasing order of frequency by body system:

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal perforation, hematemesis, hematachezia, weight loss, gastrointestinal ulceration, peritonitis, abdominal pain, hypersalivation, nausea

Urinary: elevated BUN, elevated creatinine, polydypsia, polyuria, hematuria, urinary incontinence, proteinuria, kidney failure, azotemia, urinary tract infection
Neurological/Behavioral/Special Sense: depression/lethargy, ataxia, seizures, nervousness, confusion, weakness, hyperactivity, tremor, paresis, head tilt, nystagmus, mydriasis, aggression, uveitis

Hepatic: elevated ALP, elevated ALT, elevated bilirubin, decreased albumin, elevated AST, icterus, decreased or increased total protein and globulin, pancreatitis, ascites, liver failure, decreased BUN

Hematological: anemia, neutrophilia, thrombocytopenia, neutropenia

Cardiovascular/Respiratory: tachypnea, dyspnea, tachycardia

Dermatologic/Immunologic: pruritus, fever, alopecia, moist dermatitis, autoimmune hemolytic anemia, facial/muzzle edema, urticaria

In some cases, death has been reported as an outcome of the adverse events listed above.

Contact Information: To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Pegasus Laboratories, Inc. at 1-800-874-9764 or www.prnpharmacal.com. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Information For Dog Owners: Firocoxib Chewable Tablets for Dogs, like other drugs of its class, is not free from adverse reactions. Owners should be advised of the potential for adverse reactions and be informed of the clinical signs associated with drug intolerance. Adverse reactions may include vomiting, diarrhea, decreased appetite, dark or tarry stools, increased water consumption, increased urination, pale gums due to anemia, yellowing of gums, skin or white of the eye due to jaundice, lethargy, incoordination, seizure, or behavioral changes.

Serious adverse reactions associated with this drug class can occur without warning and in rare situations result in death (see Adverse Reactions). Owners should be advised to discontinue Firocoxib Chewable Tablets for Dogs and contact their veterinarian immediately if signs of intolerance are observed. The vast majority of patients with drug related adverse reactions have recovered when the signs are recognized, the drug is withdrawn, and veterinary care, if appropriate, is initiated. Owners should be advised of the importance of periodic follow up for all dogs during administration of any NSAID.

Clinical Pharmacology: Mode of action: Firocoxib Chewable Tablets for Dogs is a cyclooxy-genase-inhibiting (coxib) class, non-narcotic, non-steroidalanti-inflammatory drug(NSAID) with anti-inflammatory and

analgesic properties.There are two main cyclooxygenase enzymes, COX-1 and COX-2, and a newly discovered third enzyme, COX-3, which has yet to be fully characterized.[1] Cyclooxygenase-1 (COX-1) is the enzyme responsible for facilitating constitutive physiologic processes, e.g., platelet aggregation, gastric mucosal protection, and renal perfusion.[2] It also is constitutively expressed in the brain, spinal cord, and reproductive tract.[3] Cyclooxygenase-2 (COX-2) is responsible for the synthesis of inflammatory mediators,but it is also constitutively expressed in the brain, spinal cord and kidneys.[4,5,6] Cyclooxygenase-3 (COX-3) is also constitutively expressed in the canine and human brain and also the human heart.[7] Results from in vitro studies showed firocoxib to be highly selective for the COX-2 enzyme when canine blood was exposed to drug concentrations comparable to those observed following a once daily 5 mg/kg oral dose in dogs.[8] However, the clinical significance of these findings has not been established.

Effectiveness: Two hundred and forty-nine dogs of various breeds, ranging in age from 11 months to 20 years, and weighing 13 to 175 lbs, were randomly administered firocoxib or anactive control drug in two field studies. Dogs were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall improvement in a non-inferiority evaluation of firocoxib compared with the active control. At the study's end, 87%of the owners rated firocoxib-treated dogs as improved. Eighty-eight percent of dogs treated with firocoxib were also judged improved by the veterinarians. Dogs treated with firocoxib showed a level of improvement in veterinarian-assessed lameness, pain on palpation, range of motion, and owner-assessed improvement that was comparable to the active control. The level of improvement in firocoxib-treated dogs in limb weight bearing on the force plate gait analysis assessment was comparable to the active control. In a separate field study,two hundred fifty-eight client-owned dogs of various breeds, ranging in age from 10.5 weeks to 16 years and weighing from 7 to168 lbs,were randomly administered firocoxib or a control (sham-dosed-pilled) for the control of post operative pain and inflammation associated with surgery (e.g. ovariohysterectomy, abdominal cryptorchidectomy, splenectomy, cystotomy) or major external surgeries (e.g. mastectomy, skin tumor removal ≥8 cm). The study demonstrated that firocoxib-treated dogs had significantly lower need for rescue medication than the control (sham-dosed-pilled) in controlling postoperative pain and inflammation associated with soft-tissue surgery.

A multi-centerf ield study with 226 client-owned dogs of various breeds, and ranging in age from 1 to11.9 years in the firocoxib-treatedgroups and 0.7 to 17 years in the control group was conducted. Dogs were randomly assigned to either the firocoxib or the control (sham-dosed-pilled) group for the control of postoperative pain and inflammation associated with orthopedic surgery. Surgery to repair a ruptured cruciate ligament included the following stabilization procedures: fabellar suture and/or imbrication, fibular head transposition, tibial plateau leveling osteotomy (TPLO), and 'over the top' technique. The study (n = 220 for effectiveness) demonstrated that firocoxib-treated dogs had significantly lower need for rescue medication than the control (sham-dosed-pilled) in controlling postoperative pain and inflammation associated with orthopedic surgery.

Animal Safety: In a target animal safety study, firocoxib was administered orally to healthy adult Beagle dogs (eight dogs per group) at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated dose of 5 mg/kg, there were no treatment related adverse events.

Decreased appetite, vomiting, and diarrhea were seen in dogs in all dose groups, including unmedicated controls, although vomiting and diarrhea were seen more often in dogs in the 5X dose group. One dog in the 3X dose group was diagnosed with juvenile polyarteritis of unknown etiology after exhibiting recurrent episodes of vomiting and diarrhea, lethargy, pain, anorexia, ataxia, proprioceptive deficits, decreased albumin levels, decreased and then elevated platelet counts, increased bleeding times, and elevated liver enzymes. On histopathologic examination, a mild ileal ulcer was found in one 5X dog. This dog also had a decreased serum albumin which returned to normal by study completion. One controland three 5X dogs had focal areas of inflammation in the pylorus or small intestine. Vacuolization without inflammatory cell infiltrates was noted in the thalamic region of the brain in three control, one 3X, and three 5X dogs. Mean ALP was within the normal range for all groups but was greater in the 3X and 5X dose groups than in the control group. Transient decreases in serum albumin were seen in multiple animals in the 3X and 5X dose groups, and in one control animal.

In a separate safety study, firocoxib was administered orally to healthy juvenile (10-13 weeks of age) Beagle dogs at 5, 15, and 25 mg/kg (1, 3, and 5 times the recommended total daily dose) for 180 days. At the indicated (1X) dose of 5 mg/kg, on histopathologic examination, three out of six dogs had minimal periportal hepatic fatty change. On histopathologic examination, one control, one 1X, and two 5X dogs had diffuse slight hepatic fatty change. These animals showed no clinical signs and had no liver enzyme elevations. In the 3X dose group, one dog was euthanized because of poor clinical condition (Day 63). This dog also had a mildly decreased serum albumin. At study completion, out of five surviving and clinically normal 3X dogs, three had minimal periportal hepatic fatty change. Of twelve dogs in the 5X dose group, one died (Day 82) and three moribund dogs were euthanized (Days 38, 78, and 79) because of anorexia, poor weight gain, depression, and in one dog, vomiting. One of the euthanized dogs had ingested a rope toy. Two of these 5X dogs had mildly elevated liverenzymes.At necropsy all fiveof the dogs that died or were euthanized had moderate periportal or severe panzonal hepatic fatty change; two had duodenal ulceration; and two had pancreatic edema. Of two other clinically normal 5X dogs (out of four euthanized as comparators to the clinically affected dogs), one had slight and one had moderate periportal hepatic fatty change. Drug treatment was discontinued for four dogs in the 5X group. These dogs survived the remaining 14 weeks of the study. On average, the dogs in the 3X and 5X dose groups did not gain as much weight as control dogs. Rate of weight gain was measured (instead of weight loss) because these were young growing dogs. Thalamic vacuolation was seen in three of six dogs in the 3X dose group, five of twelvedogs in the 5X dose group, and to a lesser degree in two unmedicated controls. Diarrhea was seen in all dose groups, including unmedicated controls.

In a separate dose tolerance safety study involving a total of six dogs (two control dogs and four treated dogs), firocoxib was administered to four healthy adult Beagle dogs at 50 mg/kg (ten times the recommended daily dose) for twenty-two days. All dogs survived to the end of the study. Three of the four treated dogs developed small intestinal erosion or ulceration. Treated dogs that developed small intestinal erosion or ulceration had a higher incidence of vomiting, diarrhea, and decreased food consumption than control dogs. One of these dogs had severe duodenal ulceration, with hepatic fatty change and associated vomiting, diarrhea, anorexia, weight loss, ketonuria, and mild elevations in AST and ALT. All four treated dogs exhibited progressively decreasing serum albumin that, with the exception of one dog that developed hypoalbuminemia, remained within normal range. Mild weight loss also occurred in the treated group. One of the two control dogs and three of the four treated dogs exhibited transient increases in ALP that remained within normal range.

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

To Request a Safety Data Sheet (SDS), call 1-800-874-9764.

How Supplied: Firocoxib Chewable Tablets for Dogs is available as round, beige to tan, half-scored tablets in two strengths, containing 57 mg or 227 mg firocoxib. Each tablet strength is supplied in 60 count and 180 count bottles.

[1]Willoughby DA, Moore AR and Colville-Nash PR. COX-1, COX-2, and COX-3 and the future treatment of chronicin flammatory disease. Lancet 2000; 355: 646-648.
[2]Smith, et al. Pharmacological analysis of cyclo- oxygenase-1in inflammation. Proc. Natl. Acad. Sci. USA, Pharmacology 1998; 95:13313-13318.
[3]Jones CJ and Budsberg SC. Physiologic characteristics and clinical importance of the cyclooxygenase isoforms in dogs and cats. JAVMA 2000;217(5):721-729.
[4]Zhang, et al. Inhibition of cyclo-oxygenase-2 rapidly reverses inflammatory hyperalgesia and prostaglandin E2 production. JPET 1997;283:1069-1075.
[5]Jones and Budsberg, pp. 721-729.
[6]Zhang, et al. pp. 1069-1075.
[7]Chandrasekharan NV, Dai H, et al. COX-3, a cyclo-oxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure and expression. Proc. Natl. Acad. Sci. USA 2002; 99(21):13926-13931.
[8]Dataon file with the NADA141-230.

Approved by FDA under ANADA # 200-751

Manufactured by:
Pegasus Laboratories, Inc.
Employee-Owned
Pensacola, FL 32514

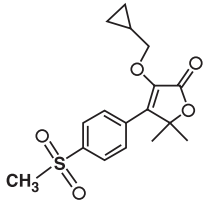
Sē•Qual™
PRODUCTS
By PRN™ Pharmacal

FIROCOXIB TABLETS FOR HORSES

For oral use in horses only.

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

Description:
Firocoxib Tablets for Horses belongs to the coxib class of non-narcotic, non-steroidal anti-inflammatory drugs (NSAIDs). Firocoxib is a white crystalline compound described chemically as 3 (cyclopropylmethoxy)-4-(4-methylsulfonyl)phenyl)-5, 5-dimethylfuranone. The empirical formula is $C_{17}H_{20}O_5S$, and the molecular weight is 336.4 g/mol. The structural formula is shown below:



Indications:
Firocoxib Tablets for Horses are administered once daily for up to 14 days for the control of pain and inflammation associated with osteoarthritis in horses.

Dosage and Administration:
Always provide the Client Information Sheet with the prescription. The recommended dosage of Firocoxib Tablets for Horses is one 57 mg tablet administered orally to horses weighing 800 – 1300 lbs, once daily for up to 14 days.
For ease of administration, Tablets for Horses may be given with food.

The overall duration of treatment with any firocoxib formulation in horses, including tablets, injection or oral paste should not exceed 14 days. Please see the package insert for firocoxib injection or oral paste for appropriate prescribing information for those formulations.

Contraindications:
Horses with a hypersensitivity to firocoxib should not receive Firocoxib Tablets for Horses.

Warnings:
For use in horses only. Do not use in horses intended for human consumption. Store Firocoxib Tablets for Horses out of the reach of dogs and other pets in a secured location in order to prevent ingestion or overdose.

Human Warnings: Not for use in humans. Keep this and all medications out of the reach of children. Consult a physician in case of accidental ingestion by humans.

Precautions:
Horses should undergo a thorough history and examination before initiation of NSAID therapy. Appropriate laboratory tests should be conducted to establish hematological and serum biochemical baseline data before and periodically during administration of any NSAID. Clients should be advised to observe for signs of potential drug toxicity and be given a Client Information Sheet with each prescription. See Information for Owner or Person Treating Horse section of this package insert.

Treatment with Firocoxib Tablets for Horses should be terminated if signs such as inappetence, colic, abnormal feces, or lethargy are observed.

As a class, cyclooxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal, and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Horses that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for adverse events are those that are dehydrated, on diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached or avoided. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such anti-prostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since many NSAIDs possess the to produce gastrointestinal ulcerations and/or gastrointestinal perforation, concomitant use of Firocoxib Tablets for Horses with other inflammatory drugs, such as NSAIDs or should be avoided.

The concomitant use of protein bound drugs with Firocoxib Tablets for Horses has not been studied in horses. The influence of concomitant drugs that may inhibit the metabolism of Firocoxib Tablets for Horses has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

The safe use of Firocoxib Tablets for Horses in horses less than one year in age, horses used for breeding, or in pregnant or lactating mares has not been evaluated.

Consider appropriate washout times when switching from one NSAID to another NSAID or corticosteroid.

Adverse Reactions:
The safety and effectiveness of firocoxib tablets was established in a relative bioavailability study comparing firocoxib tablets and firocoxib oral paste. Therefore, additional field studies were not performed to support the effectiveness of firocoxib tablets.

In controlled field studies, 127 horses (ages 3 to 37 years) were evaluated for safety when given oral paste at a dose of 0.045 mg/lb (0.1 mg/kg) orally once daily for up to 14 days. The following adverse reactions were observed. Horses may have more than one of the observed adverse reactions during the study.

Table 1: Adverse Reactions Seen in the U.S. Field Studies with firocoxib oral paste:

ADVERSE REACTIONS	Firocoxib n = 127	Active Control n = 125
Abdominal pain	0	1
Diarrhea	2	0
Excitation	1	0
Lethargy	0	1
Loose stool	1	0
Polydipsia	0	1
Urticaria	0	1

In these field trials, firocoxib oral paste was safely used concomitantly with other therapies, including vaccines, anthelmintics, and antibiotics. The safety data sheet (SDS) contains more adverse events, for technical assistance, or to obtain a copy of the SDS, contact Pegasus Laboratories at 1-800-874-9764. For additional information about adverse drug reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Information for Owner or Person Treating Horse:
A Client Information Sheet should be provided to the person treating the horse. Treatment administrators and caretakers should be aware of the potential for adverse reactions and the clinical signs associated with NSAID intolerance. Adverse may include erosions and ulcers of the gums, tongue, lips and face, weight loss, colic, diarrhea, or icterus. Serious adverse reactions associated with this drug class can occur without warning and, in some result in death. Clients should be advised to discontinue NSAID therapy and contact their veterinarian immediately if any of these signs of intolerance are observed. The majority of patients with related adverse reactions recover when the signs are recognized, drug administration is stopped, and veterinary care is initiated.

Clinical Pharmacology:
Relative Bioavailability Study

A pharmacokinetic study was conducted to compare the relative bioavailability of an oral firocoxib tablet containing 57 mg firocoxib to the approved paste formulation. The criteria for the Test/Reference (T/R) ratios and the 90% Confidence Intervals (CI) of tablets (test product) were adjusted on the basis of the safety and effectiveness data for the oral paste (reference product). The lower bound of the 90% CI for effectiveness was defined by the minimal effective plasma concentration in the study used to support the dosage characterization of oral paste. Effectiveness was based upon the area under the plasma drug concentration-time curve to the last quantifiable concentration (AUClast), with the effectiveness criteria set at a T/R ratio of greater than or equal to 0.77 and a corresponding lower bound for the 90% CI set at 0.71. The upper bound of the 90% CI for safety was defined by the minimum safe plasma concentration (Cmax) in the study used to establish a margin of safety for firocoxib oral paste. Based upon that margin of safety, product safety was defined as a T/R of less than or equal to 1.53, with a corresponding upper bound for the 90% CI of 1.71.

The relative bioavailability study was a randomized, two-period, two sequence crossover study in thirty horses. Each horse received a single tablet (57 mg firocoxib) and a single tube of paste (56.7 mg Blood samples were collected at 15 minutes, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 32, 48, 72, 96 and 120 hours following each treatment. Samples were analyzed by LC-MS/MS for firocoxib concentrations. The results of the relative bioavailability study are summarized in Table 2. The Cmax and AUClast of firocoxib tablets were within the adjusted 90% CI for safety and effectiveness and met the criteria established for successfully demonstrating that firocoxib tablets will be safe and effective. Therefore, firocoxib tablets and firocoxib oral paste are acceptable as pharmaceutical alternatives.

There was a substantial difference in the Tmax (time to maximum plasma concentration) between oral paste and firocoxib tablets. The Tmax ranged from 0.25-4 hours for firocoxib oral paste and 0.25-12 hours for firocoxib tablets. The difference in the rate and extent of absorption was greatest within the first three hours after administration. The mean terminal elimination half-life of firocoxib oral paste (45.45 hours) was similar to that of firocoxib tablet (44.49 hours).

Table 2: Relative Bioavailability Results for firocoxib oral paste (reference) and firocoxib tablets (tests) (n=30 horses)

Parameter	Units	Reference Geometric Mean	Test Geometric Mean	Test/ Reference	Lower 90% CI	Upper 90% CI
Cmax	ng/mL	78.44	58.85	0.75	67.92	82.88
AUClast	hr* ng/mL	2515.77	2336.32	0.93	86.37	99.85

Cmax = maximum observed plasma concentration

AUClast = Area Under the Curve to the last quantifiable time point

CI = Confidence Interval

The major metabolism mechanism of firocoxib in the horse is decyclopropylmethylation followed by glucuronidation of that metabolite. Based upon radiolabel studies done for the firocoxib paste formulation, the majority of firocoxib is eliminated in the urine as the decyclopropylmethylated metabolite. Despite a high degree of plasma protein binding (98%), firocoxib exhibits a large volume of distribution (mean Vd(ss) = 1652 mL/kg). The terminal elimination half-life (T1/2) in plasma averages 30-40 hours after IV, oral paste or tablet dosing. Therefore, drug accumulation occurs with repeated dose administrations and steady state concentrations are achieved beyond 6-8 daily oral doses in the horse.

Mode of Action

Firocoxib Tablets for Horses is a cyclooxygenase-inhibiting (coxib) class, non-narcotic, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic activity1 in animal models. Based on in vitro horse data, firocoxib is a selective inhibitor of prostaglandin biosynthesis through inhibition of the inducible cyclooxygenase-2-isoenzyme (COX-2)2. Firocoxib selectivity for the constitutive isoenzyme, cyclooxygenase-1 (COX-1) is relatively low. However, the clinical significance of these in vitro selectivity findings has not been established.

Effectiveness:
The effectiveness of firocoxib tablets was established in a relative bioavailability study comparing firocoxib tablets and firocoxib oral paste. Therefore, additional field studies were not performed to support the effectiveness of firocoxib tablets. (See CLINICAL PHARMACOLOGY, Relative Bioavailability Study).

Two hundred fifty-three client-owned horses of various breeds, ranging in age from 2 to 37 years and weighing from 595 to 1638 lbs, were randomly administered firocoxib oral paste or an active control drug in multi-center field studies. Two hundred forty horses were evaluated for effectiveness and 252 horses were evaluated for safety. Horses were assessed for lameness, pain on manipulation, range of motion, joint swelling, and overall clinical improvement in a non-inferiority evaluation of firocoxib oral paste compared to an active control. At study's end, 84.4% of horses treated with firocoxib oral paste were judged improved on veterinarians' clinical assessment, and 73.8% were also rated improved by owners. Horses treated with firocoxib oral paste showed improvement in veterinarian-assessed lameness, pain on manipulation, range of motion, and joint swelling that was comparable to the active control.

Animal Safety:
The safety of firocoxib tablets was supported by a relative bioavailability study comparing firocoxib tablets and firocoxib oral paste (see CLINICAL PHARMACOLOGY, Relative Bioavailability Study), pharmacovigilance information, and target animal safety data for existing firocoxib containing products in horses. No additional target animal safety studies were conducted with firocoxib tablets.

In a target animal safety study conducted to support the approval of firocoxib oral paste, firocoxib was administered orally to healthy adult horses (two male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 30 days. Administration of firocoxib at 0.3 and 0.5 mg/kg body weight was associated with an increased incidence of oral ulcers as compared to the control group, but no oral ulcers were noted with 0.1 mg/kg. There were no other drug-related adverse findings in this study.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (four males or male castrates and four females per group) at 0, 0.1, 0.3 and 0.5 mg firocoxib/kg body weight (1, 3 and 5X the recommended dose) for 42 days. Administration of firocoxib at 0.1, 0.3 and 0.5 mg/kg body weight was associated with delayed healing of pre-existing oral (lip, tongue, gingival) ulcers.

In addition, the incidence of oral ulcers was higher in all treated groups as compared to the control group. Clinical chemistry and coagulation abnormalities were seen in several horses in the 0.5 mg/kg (5X) group. One 5X male horse developed a mildly elevated BUN and creatinine over the course of the study, prolonged buccal mucosal bleeding time (BMBT), and a dilated pelvis of the right kidney. Another 5X male had a similar mild increase in creatinine during the study but did not have any gross abnormal findings. One female in the 5X group had a prolonged BMBT, bilateral tubulointerstitial nephropathy and bilateral papillary necrosis.

Tubulointerstitial nephropathy occurred in one 3X female, two 3X male horses, and the 5X female horse discussed above with the prolonged BMBT. Papillary necrosis was present in one 1X male horse and the 5X female horse discussed above. Despite the gross and microscopic renal lesions, all of the horses were clinically healthy and had normal hematology, clinical chemistry and urinalysis values.

In another target animal safety study, firocoxib was administered orally to healthy adult horses (three females, two male castrates and one male per group) at 0, 0.25 mg/kg, 0.75 mg/kg and 1.25 mg/kg (2.5, 7.5 and 12.5X the recommended dose of 0.1 mg/kg) for 92 days. An additional group of three females, two male castrates and one male per group, was dosed at 1.25 mg/kg for 92 days but was monitored until Days 147-149. There were treatment-related adverse events in all treated groups. These consisted of ulcers of the lips, gingiva and tongue and erosions of the skin of the mandible and head. Gross and microscopic lesions of the kidneys consistent with tubulointerstitial nephropathy were seen in all treated groups. Papillary necrosis was seen in the 2.5X and 12.5X groups. In addition, several 12.5X horses had elevated liver enzymes (GGT, SDH, AST and ALT). One 2.5X horse had increased urine GGT and urine protein levels which was due to renal hemorrhage and nephropathy. Gastric ulcers of the margo plicatus and glandular area were more prevalent in the 2.5X and 7.5X groups, but not seen in the 12.5X group. The group of horses that were monitored until Days 147-149 showed partial to full recovery from oral and skin ulcers, but no recovery from tubulointerstitial nephropathy.

In a target animal safety study conducted to assess the safety of firocoxib injection followed by firocoxib oral paste in the horse, thirty-two clinically healthy adult horses received firocoxib injection intravenously once daily for five days at doses of either 0 mg/kg (control group); 0.09 mg/kg (1X); 0.27 mg/kg (3X); or 0.45 mg/kg (5X the recommended dose). This was followed by once daily oral administration of firocoxib oral paste for nine days at doses of either 0 mg/kg (control group); 0.1 mg/kg (1X); 0.3 mg/kg (3X); or 0.5 mg/kg (5X the recommended dose). This sequence (five days of firocoxib injection followed by nine days firocoxib oral paste, for a total of 14 days) was repeated three times for a total treatment duration of 42 days (3X the recommended treatment duration of 14 days). Two male 5X horses demonstrated a white focus in the renal cortex which correlated with tubulointerstitial nephropathy microscopically. The presence of tubulointerstitial nephropathy was considered treatment-related. One horse from the control group and two horses from the 5X group had injection site swellings during treatment. Injection site changes characterized by inflammatory cell influx and rarely tissue necrosis were seen in all study groups including the control group. There was a dose-dependent increase in the incidence of oral ulcers and erosions. Elevated hepatic enzymes (GGT or AST) were noted in all study groups at one or more time points. One male 5X horse with an elevated GGT value on Day 42 was noted to have tubulointerstitial nephropathy at the time of necropsy. For all horses, these hepatic enzyme elevations generally returned to the reference range by the next time point.

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

How Supplied:
Firocoxib Tablets for Horses is available as round, beige to tan, half-scored tablets, containing 57 mg firocoxib. Firocoxib Tablets for Horses are supplied in 60 count bottles.

[1]McCann ME, Rickes EL, Hora DF, Cunningham PK et al. In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in cats with lipopolysaccharide-induced pyrexia. Am J Vet Res. 2005 Jul;66 (7): 1278-84.

[2]McCann ME, Anderson DR, Brideau C et al. In vitro activity and in vivo efficacy of a novel COX-2 inhibitor in the horse. Proceedings of the Academy of Veterinary Internal Medicine. 2002. Abstract 114, p.789.

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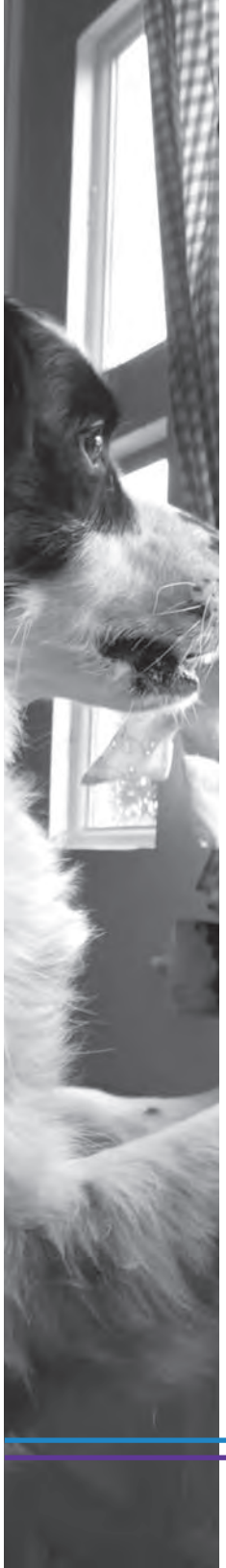

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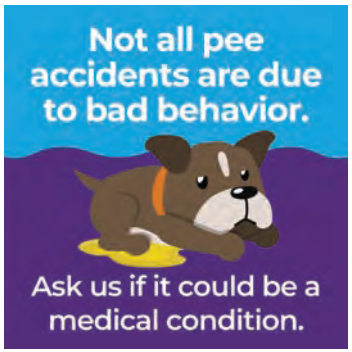

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